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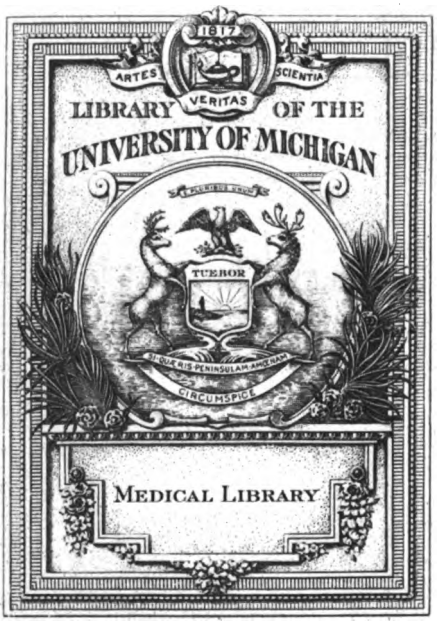

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TRANSACTIONS OF THE

SECTION ON

Pharmacology and Therapeutics

of the
American Medical Association
at the Seventy-Second Annual
Session, held at Boston, Mass.,
June 6 to 10, 1921

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LIST OF OFFICERS

Those named below have served as officers in this section. This branch of the practice of medicine has been included with other subjects in the earlier years as will be seen by the headings which denote the different section titles. The names of the officers have been taken from the public records, which are deficient in some cases. It will be appreciated if any additional data are brought to the attention of the Secretary of the American Medical Association.

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1915 This section did not meet in annual session at San Francisco.

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PROCEEDINGS OF THE SECTION

Wednesday, June 8—Afternoon

The meeting was called to order at 2 o'clock by the chairman, Dr. Leonard G. Rowntree, Rochester, Minn.

The following papers were read as a symposium on "The Value of Drugs":

Dr. Rowntree read the chairman's address, entitled "The Rôle and Development of Drug Therapy."

Dr. Lewellys F. Barker, Baltimore, read a paper on "The Value of Drugs in Internal Medicine." Discussed by Drs. Henry A. Christian, Boston, and Francis H. McCrudden, Boston.

Dr. George W. Crile, Cleveland, read a paper on "The Value of Drugs in Surgery." Discussed by Dr. John J. Gilbride, Philadelphia.

Dr. Henry F. Helmholz, Rochester, Minn., read a paper on "The Value of Drugs in Pediatrics." Discussed by Drs. F. Paul Gegenbach, Denver; Richard M .Smith, Boston, and J. I. Durand, Seattle.

Dr. William H. Wilmer, Washington, D. C.: "The Value of Drugs in Ophthalmology."

Dr. C. Macfie Campbell, Boston: "The Value of Drugs in Neurology." Discussed by Dr. Foster Kennedy, New York.

These papers were discussed as a group by Dr. Alexander Lambert, New York.

Dr. Reid Hunt, Boston, moved that the application of Prof. Albert Henry Clark, Chicago, for associate fellowship in the Scientific Assembly be approved. Seconded by Dr. Robert A. Hatcher, New York. Carried.

The chairman appointed as a nominating committee: Drs. Robert A. Hatcher, New York, Reid Hunt, Boston, and W. A. Bastedo, New York.

Dr. Robert A. Hatcher, New York, moved that the chairman appoint a committee to arrive at ideas as authentic as possible in regard to dosage in children. Seconded by Dr. Cary Eggleston, New York. Carried.

Thursday, June 9—Morning

A joint meeting was held with the Sections on Practice of Medicine and on Pathology and Physiology.

The meeting was called to order at 9:15 o'clock by the chairman of the Section on Practice of Medicine, Dr. Henry S. Plummer, Rochester, Minn.

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Dr. Henry S. Plummer, Rochester, Minn., read the address of the chairman of the Section on Practice of Medicine.

The following papers were read as a symposium on "Basal Metabolism in Clinical Medicine":

Dr. Graham Lusk, New York: "Fundamental Ideas Regarding Basal Metabolism."

Dr. Francis G. Benedict, Boston: "The Measurement and Standards of Basal Metabolism."

Dr. Walter M. Boothby, Rochester, Minn.: "The Basal Metabolic Rates in Hyperthyroidism."

Dr. James H. Means, Boston: "The Determination of the Basal Metabolism as an Aid to Diagnosis and as a Guide to Treatment in Various Diseases."

Dr. Eugene F. Du Bois, New York: "The Basal Metabolism of Fever."

These five papers were discussed by Drs. George W. Crile, Cleveland; Charles H. Mayo, Rochester, Minn.; Joseph C. Aub, Boston; Fritz Talbot, Boston; Graham Lusk, New York; Francis G. Benedict, Boston; Walter M. Boothby, Rochester, Minn.; James H. Means, Boston; Eugene F. Du Bois, New York; J. Earl Else, Portland, Ore.; Albert E. Roussel, Philadelphia, and Henry S. Plummer, Rochester, Minn.

Friday, June 10—Afternoon

The following officers were elected: chairman, Carl Voegtlin, Washington, D. C.; vice chairman, Cary Eggleston, New York; secretary, Paul D. White, Boston; delegate, Leonard G. Rowntree, Rochester, Minn.; alternate, George W. McCoy, Washington, D. C.

The following committee was appointed to investigate dosage in the treatment of children: Drs. Henry F. Helmholz, Rochester, Minn., chairman; Robert A. Hatcher, New York; Oscar M. Schloss, New York; William McKim Marriott, St. Louis, and A. D. Hirschfelder, Minneapolis.

Dr. Thomas F. Reilly, New York, read a paper on "Flatulence in the Decompensation of Cardiac Disease: Etiology and Treatment." Discussed by Drs. Frank Smithies, Chicago; Francis H. McCrudden, Boston; Anthony Bassler, New York, and Thomas F. Reilly, New York.

Dr. Benjamin H. Schlomovitz, Milwaukee, read a paper on "The Effect of Digitalis on the Response of the Cardiac Pacemaker." No discussion.

Dr. Howard M. Marvin, Boston, read a paper on "Drugs of the Digitalis Group with Special Reference to the Action of Apocynum and Convallaria." Discussed by Drs. Robert A. Hatcher, New York; Cary Eggleston, New York, and Paul D. White, Boston.

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Drs. Yandell Henderson and Howard W. Haggard, New Haven, Conn., presented a paper on "The Treatment of Carbon Monoxid Poisoning." Discussed by Drs. Royd R. Sayers, Washington, D. C., Dr. C. A. Willis, Waltham, Mass., and Yandell Henderson, New Haven, Conn.

Drs. David Marine, New York, and Oliver P. Kimball, Youngstown, Ohio, presented a paper on "The Prevention of Simple Goiter in Man." Discussed by Dr. Milton J. Rosenau, Boston.

On motion of Dr. Robert A. Hatcher, New York, a rising vote of thanks was extended to the retiring officers.

Dr. Robert A. Cooke, New York, read a paper on "The Treatment of Bronchial Asthma." Discussed by Drs. I. Chandler Walker, Boston, and Robert A. Cooke, New York.

Drs. Carl Voegtlin, M. I. Smith and James M. Johnson, Washington, D. C., presented a paper on "Therapeutic Value of Chaulmoogra Oil and Derivatives in Experimental Tuberculosis." No discussion.

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THE RÔLE AND DEVELOPMENT OF DRUG THERAPY *

L. G. ROWNTREE, M.D.
ROCHESTER, MINN.

In this symposium we are attempting to determine the value of drugs in treatment. The degree of success which will be attained obviously depends on the wisdom shown in the selection of men to represent various fields of practice. Needless to say, only those considered most eminently fitted to pass on these matters have been chosen.

Before entering on more detailed considerations, a few moments might be spent to advantage in a general survey of treatment as it exists today and in a consideration of the more important factors which have in the past, or may in the future, exercise a retarding or accelerating influence on the progress of treatment.

In considering the rôle of drugs in medicine, perspective is essential. Medical interests have become specialized to such an extent that the broad point of view is the exception. At times the sick succumb to a conflict of special interests as well as to disease. Practice is complex and each field so intricate that the specialist, seeing through his own glasses, centers only on part of the picture and loses sight of the patient as a whole. For true perspective we must return to Hippocrates. The father of medicine practiced prevention and cure. He was a general man. His therapeutic platform comprised several planks, among them surgery, drugs, dietary regimen, physical and psychical therapy. Recognizing the limitations of his day, he sought to assist Nature, the *vis medicatrix naturae,* and through

* Chairman's address.

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the control of the vital functions of the body to promote the natural processes of repair, thereby compelling the patient himself to participate in the cure. He kept two objects in mind, to do good or at least to do no harm. Since his day, medicine has progressed, but his point of view has not been superseded.

PREVENTIVE MEDICINE

The achievements of preventive medicine have stirred the admiration of physicians and surgeons alike. From the laying down of the laws by Moses sanitation has made great progress, but since the days of Pasteur this has been unprecedented. Within the last three centuries, the average working life of English speaking men has been doubled. By the public health service, we are protected both from within and from without. Vigilance exercised at our ports protects us from foreign born infections, and sanitation throughout the land is decimating many of our endemic diseases. So far as America and western Europe are concerned, preventive medicine is responsible for the greatest medical triumphs of all time.

CURATIVE MEDICINE

In the field of treatment come medicine, surgery, and the various specialties. This division is logical and counts for efficiency, provided the specialism does not result in loss of vision. Surgery has made almost unbelievable progress during the last century, particularly in the latter half. Many conditions, formerly considered medical, admittedly fare better now under surgical treatment. Although surgical technic has improved enormously, the greatest success of surgery rests on the use of drugs. Anesthesia, antisepsis and asepsis have made possible the achievements of surgery.

With regard to surgery, it is important to recall that it is but one form of therapy and that medical treatment applied simultaneously is often of the greatest conse-

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quence. Many conditions are still looked on as purely medical or purely surgical in which combined surgical and medical treatment is essential to the best results.

Medicine has somewhat neglected certain phases of physical and psychical therapy, and since these constitute important planks in treatment, the opportunity has been seized from without, for the establishment of certain cults. The most important so-called therapeutic cults have their foundation in one or the other of the well known, but unfortunately somewhat neglected, therapeutic principles. For their existence we as a profession are responsible. Treatment must be comprehensive and include in its armamentarium all measures capable of affording relief.

Drugs find their most extensive application in the field of medical treatment; but, to the thinking physician, treatment no longer consists merely in giving drugs or applying other measures of relief. The essence of treatment consists in recognizing the pathologic process; in understanding its causes, the mechanism involved in its production and in the development of its clinical manifestations; in knowing the character, extent, and probable outcome of the resulting functional and morphologic changes; in valuing correctly the significance of clinical and laboratory findings; in ascertaining the indications for, in knowing the mode of action of, and in applying the most effective measures for its prevention, abortion, amelioration, or cure. As medicine becomes more rational it becomes more effective, and drugs play a relatively smaller but better defined rôle. The essentials of good treatment are: correct and early diagnosis; a true conception of the cause and nature of the derangement; familiarity with the manner in which the derangement can be corrected, and the knowledge of, and ability to apply the most effective measure of relief.

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Factors Responsible for Retardation in Medicine.—Since time and space preclude anything approaching an historical review, let us consider briefly on the one hand the most important factors responsible for retarding progress, and on the other, the channels through which progress in treatment has come. Medicine marches with science. Since science is a matter of evolution, progress has come but slowly, and ignorance, always the chief barrier to progress, still prevails in proportions inverse to the advancement of science. While ignorance is negative in character, it gives free rein to many human frailties and prejudices, to credulity and superstition which admit free dissemination of falsehood, the combination standing for inertia, if not for stubborn opposition.

Belief in the supernatural origin of disease and superstition saddled the world with demons, witchcraft, spells, astral influences, magic art, and occult sciences, and resulted in treatment in the use of seals, charms, talismans, incantations and invocations. Absurdity reached its climax in the administration of drugs according to the signs of the zodiac. An inordinately credulous public and charlatanism within our ranks made possible the perpetration in the name of medicine of such hoaxes as signatures, similars, sympathetic ointments and Perkins' tractors. That this credulity still persists is evidenced by the fact that similar cults still flourish. In the development of Christian science, there is nothing surprising except that it has developed in an enlightened age, rather than in the dark ages. From this we learn that scientific enlightenment has not penetrated deeply into the masses and that further instruction of the public is sorely needed in matters pertaining to medicine and sciences.

Failure to appreciate duly the self limited character of the majority of diseases, that is, to appreciate the *vis medicatrix naturæ*, of Hippocrates, has constituted a fundamental oversight and has made possible the

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many systems within and the many cults without, which have obstructed the road of medicine. Therapeutic investigation, unless adequately controlled, leads usually to false doctrines.

In the final analysis it is seen that the fundamental factors responsible for the tardiness of medical progress have been: (1) the inadequacy of science during its early period of development, to cope with the complex problems of the human organism and with the processes of life and of disease; (2) the incorrect approach to the subject, that is, the employment solely of speculation uncontrolled by observation and experimentation. Our forefathers erred in accepting supernatural influences as the cause of disease, in adopting a speculative philosophy instead of investigation and in the employment of measures of relief, about which they knew little, for diseases about which they knew less.

THE CHANNELS THROUGH WHICH PROGRESS IN TREATMENT HAS COME

Progress comes through investigation, but to the public generally, medical investigation makes no great appeal. The research worker is commonly regarded as impractical, yet the routine practice of today is based on the investigation of yesterday. Wassermann tests, spinal fluid studies, renal functional tests and the use of antitoxins, of glandular extracts and of arsphenamin constitute substantial phases of medical practice today, yet we did not employ any of them a generation ago. The public and many physicians fail to recognize that progress comes through investigation, that practice is based on investigation, and that medical investigation means better care of the sick, greater public health, and happier communities.

1. *The Evolution of Science and the Adoption in Medicine of Scientific Methods.*—With Harvey commences experimental medicine. Demonstration and proof were subsequently demanded, theories and

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authorities failing longer to satisfy the profession. The "Anatomical Exercise on the Motion of the Heart and Blood in Animals," 1628, ushers in a new physiology and the science of medicine. The profession was loath to accept it; but Harvey defended his thesis despite bitter opposition, and in so doing demonstrated for all time the advantages of the experimental method.

But in the seventeenth century, medicine probably profited as much from without as from within. Not alone were experiment and demonstration needed but also training in methods of thought. This was supplied by Bacon [1] and Descartes, the former formulating "The Principles of Inductive Science," and the latter clearly distinguishing the materialistic from the vitalistic. Galileo was creating the sciences of physics and mathematics while Sanatorius, through his assistance, was applying the thermometer and the scales to physiology. Borelli was utilizing mechanics and physics in investigations of the mechanics of motion. In other words, science was in the making and the instruments and methods of science were coming into general use in medicine. Alchemy was giving way to chemistry. Iatro chemistry, mathematics, and physics were laying the foundation of a new science and this in turn was permeating medicine. Medicine passed beyond the "conjectural art" of Celsus into the realm of science.

2. *Development of Clinical Medicine.*—Through following in the steps of Hippocrates, Sydenham became the father of clinical medicine. Observation and careful clinical records resulted in the recognition of new diseases and in the clear differentiation of known diseases. His teachings pervaded the whole realm of clinical medicine and constituted a great impetus, while the contributions of Auenbrugger, Corvissart, and

1. Macaulay has discussed the nature of the services rendered society by Bacon. He says: "It was not by furnishing philosophers with rules for performing the inductive process well, but by furnishing them with a motive for performing it well, that he conferred so vast a benefit on society."

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Laennec, placed physical diagnosis on a firm basis. Diagnosis improved as the result of better histories and clinical records, more thorough physical examinations, and appropriate laboratory studies. The fundamental sciences developed and shed much light on the nature of pathologic processes. As a result, disease was recognized earlier, was understood better, and was treated on more rational lines.

3. *The Development of Pharmacology.*—Although the use of drugs comes down from antiquity, the science of pharmacology is of recent development. Magendie, a pupil of Bichat, fired by his spirit, accomplished for treatment what Bichat had accomplished for pathology, namely laid the cornerstone of an underlying science. In his epoch making investigations, his object was to ascertain the seat of action of the drug, and in his experiments he located the seat of action of upas (strychnin) in the spinal cord. The next step was taken by a pupil of Magendie, Claude Bernard, who, in 1844, localized the action of curare in the neuromuscular endings. Schmeideburg next entered the field and studied the action of drugs on the frog's heart. He and his pupils exercised a great influenze on pharmacology and have been largely responsible for its present state of development.

Pharmacology is the science of the action of drugs. It utilizes the tools of science, observation, investigation, experimentation, standards and measurement. It ascertains facts concerning changes in function wrought through the action of drugs, determines the seat of action and the mechanism whereby changes are effected and not infrequently sheds light on the nature of both physiologic and pathologic processes. It has resulted in more rational drug therapy and in the deletion of many drugs and much empiricism. More than any other factor it has established dosage and channels of administration.

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4. *The Relation of Chemical Constitution to Pharmacologic Action.*—To permit action of drugs; the living cell and the chemical molecule must come in contact. The cell may be looked on as the participating seat of the microchemical reactions. In it are chemicals undergoing reactions which result in the development of forces, and to it are constantly added new chemicals resulting in modification of reactions and in gross modifications of physiologic functions and properties.

In 1859, Stahlschmidt demonstrated that strychnin loses its tetanizing action when a methyl group is introduced and that the new compound assumes a curare-like action. Crum, Brown and Fraser, in 1868, in view of the ammonium base formed in this reaction, investigated other similar bases derived from alkaloids, brucine, morphin and thebaine and discovered that all quaternary ammonia bases paralyze motor nerve endings, thus exerting a curariform action. This spoch making discovery called attention to the relation of pharmacologic action to chemical constitution and constituted the beginning of rational synthetic pharmacology.

Ehrlich, in 1898, enumerated five important instances selected from the whole of therapy in which a relationship was established between chemical constitution and pharmacologic action. Since that time, this number has been multiplied many fold and innumerable chemical compounds have been synthesized in the effort to obtain drugs with specific properties. Many drugs have been analyzed, that is, dissected into their component parts and the specific action of the drug as a whole determined as a property of one of its radicals. Thus Ehrlich was able to synthesize arsphenamin, and thus Macht recognized the importance of the benzyl group in opium. Such discoveries have resulted in the introduction into clinical practice of many drugs, among them, arsphenamin, neo-arsphenamin, benzyl alcohol, and benzyl benzoate.

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Many isolated instances of the effects of chemical constitution and of chemical configuration on pharmacologic action are known. However, in a broad sense, progress has not been great as yet. We have, as it were, but a vision of the promised land.

5. *The Discovery of Micro-Organisms and of Their Relation to Disease.*—The discoveries of Pasteur revolutionized medical conceptions and doctrines and resulted directly in the development of bacteriology and immunology. They are responsible also for many effective public health measures, and underlie the principles of aseptic and antiseptic surgery.

Immunotherapy, at present, is sharply differentiated from pharmacology. It deals largely with the nature of infecting agents, with the mechanism of infection and with specific immunity reactions. Immunity processes are undoubtedly chemical or physiochemical in character, but are as yet but little understood. As more light is shed on these subjects, immunology and pharmacology will probably become more closely allied.

6. *Aseptic and Antiseptic Surgery.*—Following the work of Pasteur and the adoption of the germ theory, Lister applied antiseptic principles to surgery. Aseptic surgery, in reality a form of preventive medicine, proved so effective that antisepsis did not receive the attention it actually merited. With the advent of war came the need for antiseptic surgery. For obvious reasons, asepsis was unattainable and Lister's doctrines and methods were tried but with disappointing results. Failure at first was ascribed to technical inadequacies, but later to incorrectness of principles. Indeed, one eminent authority insisted that "the treatment of suppurating wounds by means of antiseptics is illusory, and that belief in its efficacy is founded upon false reasoning." Lister's clinical observations and experiences were forgotten, and were replaced by theories and by experiments in vitro, which failed to approach the actual conditions confronting the surgeon.

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However, the problems were attacked by Carrel and Dakin on simple grounds, by utilization of a substance, nonirritating to the tissues and with sufficient bactericidal power to kill all varieties of microbes present in wounds. Dakin set about finding such a substance and Carrel to elaborating the most effective manner of applying it. The problem was chemotherapeutic in nature. Methods such as were employed by Ehrlich were adopted, and various antiseptics were tried. The most desirable was selected, and so modified as to meet most effectively the conditions confronting the surgeon. As a result, the Carrel-Dakin method of antiseptic treatment was evolved, and the chloramines assumed a position of considerable importance in surgical practice.

7. *Specific Chemotherapy.*—The surest, and usually the shortest, approach to the specific treatment of any disease lies through the application of experimental therapy to the experimentally induced disease in animals. Thomas, of the Liverpool school of tropical medicine, used atoxyl with good results in experimental trypanosomiasis, but sought other arsenical compounds less toxic for the host and more toxic for the parasite. Ehrlich, recognizing the true constitution of atoxyl, undertook its modification, and in the course of some years produced several arsenicals less organotropic and more parasitotropic than atoxyl. His researches resulted in the discovery of arsphenamin and in its universal acceptance in medical practice. In his work, many principles were evolved which will prove of the greatest significance to further progress in the field of specific chemotherapy.

8. *Nutrition, Metabolism.*—Where there is life there is chemical reaction, the sum total of which we term metabolism. Derangements of metabolism retult often in the appearance of disease. The nature of the derangement has been ascertained in some instances. Through the development of knowledge relating to

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metabolic diseases and to the nature and the caloric value of foodstuffs, regulation of diet has developed along rational lines and has resulted in definite control of the course of disease in many instances. Recent investigation has revealed the fact that normal control of various phases of metabolism is exercised by internal secretions or specific substances produced by the glands of internal secretion. Perversion of these secretions leads to disease. Thus, through the employment of thyroxin, myxedema readily yields to treatment and through the use of extract of the posterior lobe of the hypophysis, diabetes insipidus is readily controlled temporarily. Little is known concerning the action of drugs on metabolism, but since the synthesis of thyroxin and epinephrin has already been effected, it would appear that the day of drug control of metabolism is close at hand.

For normal metabolism the so-called vitamins are essential. Neither their character nor the mechanism of their action is known. Their withdrawal from the diet results in the appearance of one or the other of the so-called deficiency diseases, while their reintroduction into the diet, after their prolonged absence, frequently results in cure. Here again it is but a question of time before definite chemical compounds will replace the substances now classed as vitamins.

9. *Functional Conception of Disease.*—Recognition of the functional factors in disease is rapidly obtaining a strong foothold in medicine and is replacing the structural conception which by virtue of its very nature is entirely unsympathetic to drug therapy. While a knowledge of morphologic pathology is essential to medicine, it tends more to surgical treatment or to no treatment at all. However, the recent developments of pharmacology and the ascendency of physiologic and chemical trends in medicine (including pathology) have resulted in a more wholesome attitude toward drug treatment. In its beginning, at least, disease is derange-

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ment of function. Drugs cope more satisfactorily with derangements of function than with those of structure. The maintenance of function compatible with life, in spite of the existence of definite or even advanced structural changes, constitutes true therapeutic achievement.

LINES OF FUTURE DEVELOPMENT

The Broadening of the Scope of Pharmacology.—In the use of drugs, the general practitioner is the final court of appeal.[2] As a rule, however, drugs should never come into general use unless they are of unquestionable merit. The welfare of the public demands preliminary experimentation and adequate controls. The results in ten well controlled cases are of more value than the haphazard impressions from a thousand cases. The possibilities relative to the true value of drugs can be ascertained best by those trained in the field of experimental therapy. The channels through which drugs are introduced into general use are of considerable consequence. For instance, Ehrlich not only made brilliant discoveries but showed great insight in the selection of channels through which arsphenamin was safely and quickly introduced into practice.

Fundamentally, disease rests on functional and structural changes secondary to physicochemical reactions. Pharmacology deals with the influence of chemical, or if you please, physicochemical, agents, on the organism. In the past, pharmacologists have limited their activities, as a rule, to ascertaining the effect of these agents on healthy animals. It is now recognized that this was a great mistake. The transferring of results from mice to man and from arterial rings to the intact animal is not always justifiable or possible. For this the pharmacologists are not to blame, since the opportunity for studying the action of drugs in naturally induced diseases is afforded them but rarely.

2. As a matter of fact, highly trained clinicians exercise a profound influence on therapy, and it would be better if they constituted the last court of appeal.

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By training, pharmacologists are better equipped than are any other class of medical men, for ascertaining the effect of drugs on disease. But access to clinical material is usually lacking, and in consequence their training is lost to medicine so far as experimental therapy is concerned. Obviously, in this connection, the initiative must come from the clinic itself. The broadening of the scope of pharmacology, involving inclusion of experimental therapy and access to wards, would accomplish much for the advancement of medical treatment and result in an influence such as that exercised by Cushny and McKenzie in England, and Hatcher and Eggleston in this country.

Guidance in the Use of New Drugs.—Drugs enter practice through two channels, through science and through commerce. In their entrance through scientific channels exaggerated therapeutic claims are made at times, as the result of a lack of critical judgment and of adequate controls. But in their introduction through commercial channels, financial considerations and lack of true appreciation of the fundamental problems preclude unbiased evaluations. Today many proprietary drug interests are not content to supply the demand, as in olden days, but they deliberately attempt to create demand. As a result, the general practitioner is placed in a peculiar dilemma. Besieged daily by advertising matter, reeking with scientific patter, he falters between the teachings of medicine and the alluring claims of advertising agencies.

The confidence to be placed in any information depends largely on its source. Too frequently, commercial advertising is utterly misleading. It would be unfair, however, to assume that all drug advertising falls into this category for many drug houses have secured the services of medical men of excellent training and of high ideals to assist in the preparation and marketing of their products.

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In many instances, it is difficult to determine whether new medicinal articles are, or are not, of merit. To assist in this undertaking, the American Medical Association has created the Council on Pharmacy and Chemistry. It consists of a body of men selected because of their special knowledge of one or more fields of drug therapy. Originally, their functions were somewhat analogous to those of a vigilance committee. The objects of the Council are: to protect the profession and public against fraud, undesirable secrecy, and objectionable advertising in connection with proprietary medicinal articles.

The Council stands for simplicity in drug therapy and for the use of useful drugs only. To this end, it has published a small volume called "Useful Drugs" in which are presented the drugs which in the opinion of the Council merit a place in this category. The preparations listed therein should receive major consideration in all courses in pharmacology and therapeutics and also in the actual treatment of the sick as it is carried out by practitioners. In addition, the Council brings together annually, in a second volume "New and Nonofficial Remedies," such new remedies as comply with the requirements of the Council and can establish their eligibility. Admission of medicinal articles to "N. N. R." does not carry with it a recommendation on the part of the Council, but indicates only the ethical standing of the preparation.

These two small and inexpensive volumes, "Useful Drugs" and "New and Nonofficial Remedies" should form a part of every physician's library, and should serve as a guide in the use of remedies, old and new. Their widespread adoption will do much for the wiser use of drugs.

The Adoption of Sound Therapeutic Principles in Teaching and Practice.—Sound teaching regarding the nature of disease and the influence of drugs will take care of many of our present difficulties. This

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involves leadership in the realms of therapeutics as well as in the fields of physiology and pathology. Therapeutic nihilism breeds poor treatment. The failure of clinical teachers to utilize useful remedies engenders haphazard therapy in the physicians of the future. Proper teaching will prove the most effective weapon in combating the evils in advertising.

The physician must be brought to feel the responsibility for treatment as well as for diagnosis, and to accord treatment the same time and effort accorded diagnosis.

Strict attention to indications is of importance. The intelligent selection and administration of therapeutic agents, with due appreciation of the work to be accomplished and of the results to be expected, will result in greater progress. In this connection, Dr. Barker's classification of drugs into: first, those that destroy the cause; second, those that restore disturbed function; third, those that help to regulate the vital processes, and fourth, those that relieve symptoms, should prove of definite value. Treatment should be conducted as a matter of scientific investigation. Drugs should be used to accomplish certain results and the results should be checked.

The therapeutist must deal at times with intangible qualities such as strength and reserve force, and at times proof of improvement is subjective only. It cannot be emphasized too strongly, however, that therapeutic success should be measured objectively whenever this is possible. In many instances, new methods must be devised for this purpose. Graphic records, whenever possible, are of great value, especially for purposes of comparison.

Dosage and channels of administration must receive more consideration. The C/T of Ehrlich, the dose curative as related to the dose tolerated, must play an increasing rôle and will greatly modify dosage. Its application has already resulted in fundamental changes

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in the dosage of digitalis and in the relatively tremendous doses of sodium iodid now in use in the treatment of syphilis.

In the use of complex medicinal compounds, standardization is essential in order to furnish units of measurement for dosage, and its widespread adoption is only a matter of time.

The Need of a National Institute of Drug Therapy.—The complexity of the human organism, of life's processes and, to a less extent, of drugs, demands a breadth and depth in investigation, the details of which are beyond the grasp of one individual. Group investigation is as greatly needed as group practice. In chemotherapy, chemistry and experimental medicine are represented. Chemical detail is best handled by chemists, and therapeutic details by physicians and pharmacologists. Each deserves the best individual effort of specialists, but the results need correlation. A National Institute of Pharmacology and Experimental Therapeutics would prove of inestimable value to American medicine.

CONCLUSION

In drug therapy, recent progress has been both rapid and great. Much has been accomplished. Much remains to be done before medicine attains its good and converts the healing art into the healing science.

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THE VALUE OF DRUGS IN INTERNAL MEDICINE

LEWELLYS F. BARKER, M.D.
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We are now witnessing a cautious revival of the use of drugs in the treatment of disease. During the last half of the nineteenth century pharmacotherapy fell more or less into discredit, owing (1) to a reaction against the scandalous abuse of the "shotgun prescription," (2) to the general therapeutic nihilism that followed the rise of studies in pathologic anatomy, and (3) to the growing recognition of the importance of forms of therapy other than treatment by drugs. Though in some quarters the denial of pharmacotherapy was pushed to extremes, it is now generally admitted that the movement against the indiscriminate and noncritical use of drugs, to the relative exclusion of other and often more efficacious methods of therapeutic intervention, was necessary and timely, in order that the more rational therapy of our period might emerge.

In the therapy of today, based on more accurate diagnosis and on enlarged conceptions of pathologic physiology, etiology and pathogenesis, a new hopefulness prevails. We make use now of a host of methods that are found to be trustworthy for healing, for palliating and for preventing. Along with diet, baths, climate, air, light, heat, exercise, massage, electricity, roentgen rays, radium, serums, vaccines, mechanical appliances, surgery, nursing, and psychic and social influences, drugs are gradually finding their proper place in the therapeutic armamentarium of the medical

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practitioner. For among the drugs of various sorts, including both natural substances and pure chemicals provided by separation or by synthesis, there are agents than can now be employed with great confidence and often with the happiest results.

DUTY OF THE INTERNIST

In the management of patients and in the treatment of their diseases, it is our duty as physicians to see to it that we do not neglect to make application of any of the agents at our disposal that may reasonably be expected to help. Briefly to survey the help offered to the physician in his daily work by modern pharmacotherapy is the object of the present symposium. The time allotted will, of course, not permit of any detailed discussion of the use of single drugs. It is, I take it, the intention of those who planned the symposium that it should deal rather with the general principles that underlie the use of drugs in therapy, and with certain examples of the application of these principles in practice. Others are to speak of the use of drugs by surgeons and by specialists; this paper has to do with their use by the internist.

Man desiring to help his suffering fellow man must not lack—indeed, has never lacked—courage. Think, for example, of the boldness of the surgeon who annihilates the consciousness of his patient and then, without trepidation, cuts into the abdomen, or excises a goiter, or removes a brain tumor! The physician also must have bravery, one might almost say audacity, when he attempts, by the use of a drug, to intervene favorably in the disturbed physical, chemical and biologic processes of the human body in disease.

COMPLEXITY OF CHEMICAL PROCESSES

Man's body is the most marvelous chemical laboratory in the world, a laboratory made up of several thousand billions of separate work rooms, in each of

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which the amount and kinds of work done differ somewhat from those in each of the others. No two liver cells, probably, are precisely alike in their chemical activities. In a single mucous membrane, the chemistry of the constituent gland cells differs markedly from the chemistry of the constituent nerve cells, connective tissue cells and smooth muscle cells. Within the channels of communication that carry fluids and solids about the great laboratory from work room to work room, chemical changes are constantly going on in the transported materials. Even the walls, the beams and the furniture of the billions of work rooms are themselves constantly undergoing chemical change. We are awed enough by the complexity of the chemical processes that go on in health; but let us not forget that in the diseased body, which is the province of the pharmacotherapist, this complexity becomes manifold. Into this apparently infinite welter of chemical transformations (though, in reality, orderly and ultimately knowable) goes the drug that the physician administers in the hope of curing, regulating or ameliorating. Its administration surely signifies courage on the part of the physician who has such a conception of the body's chemistry. The task he attempts is truly Promethean. Is it not to try "to defy Power, which seems omnipotent?"

THE DEVELOPMENT OF PHARMACOTHERAPY

Man's needs have been so urgent, however, that medical men everywhere, and at all times, have not hesitated to defy powers when they seemed malevolent; and drug therapy has, despite its besetting difficulties, become one of the successful methods by which medicine "folds over the world its healing wings."

The clinical experience of the centuries slowly supplied an important body of facts regarding the nature of disease and man's power to control it, but the formation of true guiding principles for pharmacotherapy had to await the rise of modern science. More of value

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has been learned regarding rational treatment by the use of drugs in the last fifty years, perhaps, than in all the centuries that preceded; for, during the last fifty years, we have gained entirely new conceptions of the nature and causes of disease.

Through chemical, physiologic, psychologic, pathologic and clinical studies we have learned much regarding pathogenesis, that is to say regarding the chains of changes in the body that follow on injuries of various sorts. Synthetic chemistry has supplied us with a host of new substances for trial as remedies. The new sciences of pharmacology and toxicology have revealed to us the mode of action of drugs and poisons, and medical students are observing for themselves, in our pharmacologic laboratories, the physiologic effects that follow the introduction of foreign substances into the animal body, and they measure some of these effects with instruments of precision. Knowing only too well that, in the diseased body, drugs often act in an unexpected manner, in ways very different from those in which they act in the healthy body, clinicians have wisely seen that the pharmacology of the laboratory, though of great value for the general advance of scientific therapy, cannot take the place of accurate clinical observation. It can do much to guide therapeutic effort and to supply criteria for judging of its effects, but the final and crucial test of the value of any therapy is that of actual clinical experience. The clinic can help the laboratory, and the laboratory the clinic; but each has its independent domain that should be conscientiously worked and zealously safeguarded.

THE NEW EXPERIMENTAL SCIENCES

Recently, laudable attempts partially to bridge the gap between the pharmacologic laboratory and the clinic, in the interests of pharmacotherapy, have been observable in the work of the new sciences of experimental pathology and experimental therapy, especially

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experimental substitution therapy, and experimental antiparasitic therapy (immunotherapy, serotherapy and chemotherapy).

Workers in these new sciences reproduce certain sharply circumscribed syndromes in experimental animals and then study various forms of treatment experimentally, analyzing the effects of the measures tried. With the advent of experimental pathology and experimental therapy, we can hope for the rapid development of a systematic science of therapy; and though the transfer of results of experiments in treatment of sick animals to treatment of the sick human being will always mean a leap from the known to the unknown, still this transit will from now on be made with ever lessened danger. New drugs and chemicals will in the future be thoroughly and reliably tested, not only in pharmacologic laboratories on healthy animals, but, as far as possible, also in laboratories of experimental pathology and therapy, on animals in which special diseases have been induced, before we shall feel justified in making trial of them in the treatment of sick human beings.

CLASSES OF PHARMACOTHERAPY

Now that physicians generally understand that, in all diseases or pathologic processes, they have to deal with modifications of normal (or physiologic) processes that depend on definite disease causes, modifications, moreover, that are beyond the self-regulating capacity of the organism to keep within those limits of functional activity that we observe in "health," the internist can classify his pharmacotherapeutic efforts according to the kind of effect he desires to produce. Thus, (1) he may try with a drug to remove the cause of the disease or to render it harmless (etiologic pharmacotherapy); or (2) he may use a drug that will help directly to restore a pathologically disturbed function to normal (functional pharmacotherapy); or (3) he may administer substances that will aid the organism in its modes

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of reaction against the disease-cause (regulatory pharmacotherapy); or, finally, (4) he may employ drugs merely to relieve single troublesome symptoms (symptomatic pharmacotherapy). Internists who, after thorough and complete diagnostic studies, carefully consider these several indications (etiologic, functional, regulatory and symptomatic) should achieve in their pharmacotherapy the highest possible success.

ETIOLOGIC PHARMACOTHERAPY

Pharmacotherapy is seen at its best when, through the use of a drug, the cause of a disease is removed or rendered harmless (etiologic pharmacotherapy) before the patient has sustained irreparable injuries. The organism can then right itself, so that its activities can resume their normal or physiologic course. As our knowledge of disease causes steadily undergoes increase, ever more maladies will be made accessible to etiologic therapy. Physicians of all times have considered the causal indication when they removed harmful substances from the stomach by emetics, such as mustard or ipecac, or from the intestine by purgatives, such as castor oil, calomel or magnesium sulphate. The greatest successes in causal therapy have, however, been achieved by using drugs that kill living animal or vegetable parasites within the body, or that drive them from the body into the world outside. The use of oleoresin of male fern against tapeworm, of santonin against roundworms, and of oil of chenpodium against hookworms, are paradigms of antiparasitic pharmacotherapy. The parasites of malaria were killed by the quinin contained in cinchona long before we knew that the malarial fevers were parasitic in origin. Pathogenic amebas in the intestine can be killed off by means of emetin hydrochlorid. The fungi that cause blastomycosis and sporotrichosis die when subjected to the influence of the iodids. Noteworthy triumphs have recently been scored also by etiologic chemotherapy directed

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against certain parasites (trypanosomes, spirochetes and spirilla) that cause African sleeping sickness, syphilis, and relapsing fever. Through prolonged experimental work, parasiticides have been discovered that have a greater affinity for and toxic effect on trypanosomes and spirilla than on the body cells and organs; in other words, poisons that are more parasitotropic than organotropic can now be used to kill certain invading micro-organisms without too much injury to the invaded host. Arsphenamin and neo-arsphenamin help us greatly in the fight against syphilis, and are undoubtedly valuable additions to our pharmacopeia. With further studies of the parasitotropic qualities of various arsenical and antimonial compounds, we can reasonably hope for satisfactory means of control of a series of tropical diseases that up to recent times have defied the efforts of therapists.

In the antiparasitic treatment of diseases of bacterial origin, experimental chemotherapy has thus far been baffled. This does not mean, however, a permanent defeat. There is much to encourage investigators to continue their search for internal disinfectants that may be safely used. The body fluids and the body cells contain, and manufacture, substances that can kill bacteria. The chemical constitution of these bactericidal substances, we can feel sure, will ultimately be discovered; the substances will, later, be made synthetically and utilized in therapy. Moreover, toxic bacteriotropic substances that are foreign to the organism and innocuous for it will also doubtless be found and used. We already know that ethylhydrocuprein will kill pneumococci, though its deleterious effect on the optic nerve makes it unsafe as yet as a therapeutic agent. But who knows how soon some enterprising experimental chemotherapist may find a related pneumococcicidal substance that is less harmful to the body, just as the discovery of the relatively innocuous spirillocidal arsphenamin succeeded that of the blindness-producing atoxyl?

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FUNCTIONAL PHARMACOTHERAPY

Though less ideal and important than etiologic therapy, much good can be accomplished by the internist who, making use of a so-called functional pharmacotherapy, tries to restore to normal some function that, through disease, has become disturbed or abolished.

This can easily be made clear by citing a few examples. Thus, a patient with valvular disease of the heart may get on well for years, thanks to the reserve force of his cardiac muscle. But, sooner or later, the function of the heart muscle begins to fail, and breathlessness, tachycardia, arrhythmia, passive congestion and edema appear. In digitalis, the pharmacotherapist possesses a remedy that, properly used, will often slow the heart rate and increase the contractility and tonicity of the muscular walls of the heart so that the circulatory insufficiency will disappear. Or, a patient in whom atrial (auricular) fibrillation exists may have the normal initiation and conduction of atrial stimuli restored by means of a few doses of quinidin. Or, again, a patient whose arteries are becoming sclerotic may have spasms of the coronary vessels and the severe pain of angina pectoris that can be relieved by dissolving a tablet of glyceryl trinitrate under the tongue, which, by dilating the pathologically contracted coronary arteries, removes directly a responsible functional disturbance. Similarly, we can relax the bronchospasm of a typical attack of bronchial asthma by the injection of a few minims of a solution of epinephrin (1 : 1,000), and we can spur the atonic wall of the intestine to contract in a postoperative case by means of a hypodermic injection of solution of hypophysis (pituitary extract). In all these instances we make use of a functional pharmacotherapy.

Another example may be chosen from the field of metabolism. Thus, in gout, uric acid is not adequately excreted by the kidneys, being retained in the blood or deposited in the tissues about the joints. The function

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of uric acid excretion by the kidneys can be temporarily increased by the administration of cinchophen or neocinchophen, substances that also exert an exceptionally efficient analgesic effect in acute attacks of gout.

What we know as "organ therapy" may also be regarded as one kind of functional pharmacotherapy. If dried thyroids, for example, be given to a patient with myxedema (due to absence or defective function of the thyroid gland), the substance administered is capable of substituting for the function in abeyance and, in turn, of restoring to normal function those distant organs whose activities have undergone change through lack of the thyroid hormone.

REGULATORY PHARMACOTHERAPY

Turning next to regulatory pharmacotherapy, that form of treatment in which we administer remedies with the object of "aiding the body to react against the disease-process or the disease-cause," a good example will be seen in the pharmacotherapy of acute nephritis. In a severe glomerulonephritis, water, salt and urea are no longer adequately excreted by the kidneys, being retained in the body. The body attempts to excrete these vicariously, through the digestive tract and the skin. The physician may aid this natural reaction of the organism by using (1) a drastic purgative, like compound powder of jalap, which produces copious watery evacuations, and (2) a powerful diaphoretic, like pilocarpin nitrate, which causes free sweating. Such purgation and diaphoresis support the activities of the normal regulatory mechanisms of the body and are therefore classed as examples of "regulatory" pharmacotherapy.

In the treatment of diphtheria with antitoxin, we also employ a regulatory therapy, for, on injection of the antitoxic serum, we support the normal reaction of the organism in its effort to produce chemical substances that neutralize the toxins of the diphtheria bacilli.

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The treatment of a posthemorrhagic anemia by preparations of iron may serve as a third example of regulatory pharmacotherapy. The body reacts after severe hemorrhage by increased activity of the red bone marrow, regenerating red blood corpuscles rapidly. More iron may be required for this accelerated erythropoiesis than is available in the ordinary diet. The reactive regenerative process can be strongly favored by administering ferrous carbonate, say in the form of Blaud's pills.

SYMPTOMATIC PHARMACOTHERAPY

Symptomatic pharmacotherapy, which neither intervenes in the disease process as such nor attacks its cause, is, however, a form of therapy that is by no means to be despised. Though it is directed only toward single symptoms that injure or torment him, this therapy is hightly important for the patient, and, when successful, is the ground for much gratitude on his part. There is scarcely a symptom that is complained of by patients that physicians have not attempted to influence by pharmacotherapeutic methods. And the relief that can be afforded in many instances thoroughly justifies the attention that is given to the *indicatio symptomatica*.

It is above all in the relief of pain and of various forms of mental and bodily discomfort that this is true. We would not willingly neglect the administration of morphin in renal colic; of acetylsalicylic acid in the arthralgias; of wine or beer to paralyze certain pathologic inhibitions and to bring needed relaxation; of heroin and codein in the racking cough of pneumonia; or of the various analgesics that are effective in migraine, in neuralgias, and in the lancinating pains of tabes. Though we may deplore the abuses of alcohol as a beverage, of purgatives in habitual constipation, of sedatives in the neuroses, and of hypnotics in insomnia, we all will admit that after causal, functional and regulatory indications have been as fully met as

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our science permits of, there will be occasions when the merely symptomatic indication dare not be ignored.

CONCLUSION

It will be clear from what I have said that the internist looks on the use of drugs in therapy more hopefully now, perhaps, than ever before. Available drugs are of real value in curing, in ameliorating and in preventing disease, and new drugs that are useful are steadily being discovered.

Adequately to make use of the pharmacotherapeutic means at his disposal for meeting etiologic, functional, regulatory and symptomatic indications, the internist must, it is true, have mastery over a large body of facts. He must be well trained in normal and pathologic physiology and should have become acquainted with the known facts of etiology and pathogenesis. He should have learned in the pharmacologic laboratory the effects of the more important drugs on the normal animal body; and he should have had opportunity in the hospital wards, and in the laboratory of experimental pathology and therapy, to observe the changes that can be produced by drugs in disease. Very few have as yet had opportunity for the latter, but the medical schools should provide for it in the future.

Our teaching hospitals at present are, perhaps, more diagnostic institutes than institutes of therapy. It might, possibly, be wise to divide our medical clinics into two parts, patients entering one division for general diagnostic study and emergency measures, to be transferred afterward to the other division for full treatment, the effects of which could be carefully observed by the students.

The internist with such a training in the medical school as I have outlined will be prepared to institute a rational therapy wherever this is possible. He will know how to make a judicious use of empiric therapy when a rational foundation is lacking. As a matter of

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fact, pathology and therapy have of late years made such rapid strides that the physician can, in the majority of instances, give reasons for the therapeutic faith that is in him. For this we have to thank both the research activity of the scientific laboratories and the keen and critical observations of our better clinics.

The introduction of new therapeutic methods and new drugs can scarcely be expected from now on to be arrived at by accident, or through pure empiricism. Every new therapeutic agent should, as Magnus[1] has emphasized, be thoroughly tested in the laboratories as regards its activity and its dangers and, later, in the organized clinics, before it is introduced into general medical practice. But results in clinical experience must ever remain the final and crucial test of every form of therapy.

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ABSTRACT OF DISCUSSION

DR. HENRY A. CHRISTIAN, Boston: I wish to emphasize two statements Dr. Barker made. The first of these is, "Clinicians have wisely seen that the pharmacology of the laboratory, though of great value for the general advance of scientific therapy, cannot take the place of accurate clinical observation." The second statement is, "The final and crucial test of the value of any therapy is that of actual clinical experience." Mark the words: "accurate clinical observation" and "actual clinical experience." Herein must of necessity lie much of the progress in treatment, if progress we are to have. Let me advise you in treatment to have an intelligent skepticism in regard to treatment. This is very different from therapeutic nihilism. Be wary of the words of the itinerant drug vender and of the literature flooded in on you by the drug houses. This is not to decry the very genuine efforts that the manufacturing pharmaceutical houses are making to improve medicaments and to discover better ones. It is, however, to say: Listen an dread in a critical spirit, ready to try the new when evidence is good that it is of value, but realize that much that is printed is not based on what Dr. Barker calls accurate clinical observation, but results from a confusion as to cause and effect by reason of lack of accurate clinical observation and failure to think

1. Magnus, R.: Allgemeine Pharmakotherapie, in Krause and Garrè: Lehrbuch der Therapie der innerer Krankheiten, Jena 1:71-143, 1911.

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clearly and critically. Perhaps the best example of the worst that is being done at present lies in the literature and the claims made in so-alled studies of endocrinology, and the attempt therein to apply to unknown conditions unknown drugs with poor observation of results. Is it any surprise that the conclusions are far from sound. It is within the power of every practitioner to observe accurately and to record carefully his observations, and to contribute thereby to advance in therapy. And, perhaps, as a corollary to that, it is fair to say that a lack of advance in therapy has come in considerable part from the failure of the practitioners of the country to do these simple things. Continued improvement in medical education must of necessity furnish better practitioners more capable of carrying on these types of observations, and the result can only be improvement in our drug therapy, as well as in other methods of therapy. Finally, let me emphasize the importance of treatment. It does much good in making our patients more comfortable, and thereby it must have a very manifest effect on the course of the disease. After all, we deal with many diseases of an acute or chronic nature whose exact cause we do not know, and we are confronted with an extremely large group of patients suffering from those chronic conditions to which we probably can bring only amelioration of suffering and a retardation of the processes, and in that group symptomatic treatment is of great importance.

Dr. Francis H. McCrudden, Boston: One sentence of Dr. Barker's paper, "Our teaching hospitals at present are more diagnostic institutes than institutes of therapy," might well be made the text for many papers. Students go to the medical school to learn how to treat sick patients. In their courses in internal medicine, emphasis is laid on diagnosis, not on treatment. The wrong point of view of their function as physicians which they acquire is likely to affect their activities for a long time even after they leave school. The internist deals largely with chronic disease in which improvement in functional efficiency of the patient, rather than restoration of structural integrity, is the aim of therapeutics. An intelligent understanding of the functional therapeutics of chronic disease is much more difficult than an understanding of the theoretically more ideal direct methods of treatment. The methods of treating chronic diseases should be emphasized in the teaching of therapeutics: first, the importance of functional efficiency and, second, quantitative diagnosis, as distinguished from qualitative. As a rule, we must make the best of the organ which is structurally imperfect, and the first step in improving functional efficiency of such an organ is a recognition of the degree of impairment of function. The term "quantitative diagnosis" should, therefore, be freely employed, and the student be made to understand fully all that it implies. The next step is to improve functional

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efficiency. When equilibrium between working powers of organs and the work they are called on to do is lost, two groups of therapeutic measures are used to restore equilibrium. First, methods which stimulate organs to do better work, and, second, methods which decrease demands on organs. Rational therapeutics deals largely with questions of how and when to apply such methods. It is largely a branch of applied physiology. This is the broad point of view which should be emphasized in teaching therapeutics to students. Therapeutics should be taught in a clinic as a separate course from pharmacology, and should be the most important course in a medical school.

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THE VALUE OF DRUGS IN SURGERY

GEORGE W. CRILE, M.D.
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With increasing knowledge of the laws governing the operation of the human organism, surgeons are placing increasing dependence on methods which conserve the organism, and the use of drugs in surgery is becoming limited to those which serve this end.

As the condition of the organism as a whole depends on the state of its ultimate component units, the cells, it follows that the determination of methods of value to the organism depends on the laws which govern the cell.

LAWS GOVERNING THE CELLS

The cells whose condition is of primary importance to the surgeon are the nerve cells, the liver cells, the kidney cells and the heart muscle cells. These cells are all governed by identical laws, which are as exact as the laws of physics. A study of the structure of the cell gives the clue to its prime function and therefore to the methods whereby it may be conserved and repaired. The nucleus is separated from the body of the cell, and the cell is separated from the neighboring cells by a selective semipermeable membrane. The nucleus and the body of the cell cannot both be best stained by the same medium, but differential stains are required, that is, the nucleus takes an acid stain, and the remainder of the cell takes a basic or alkaline stain.

The cell content consists in the main of colloidal particles suspended in water. Two colloids of different reactions separated by a semipermeable membrane constitute an electric battery. A cell, therefore, is a diminutive electrochemical unit or battery.

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It follows that the vitality of the cell must depend on three principal factors: namely, oxidation, the maintenance of the normal state of permeability of the cell membranes, and the maintenance of the normal acid-alkali balance between the body of the cell and the nucleus.

Of these three, the principal source of energy is oxidation. Oxidation produces acids. It follows that the state of the acid-alkali balance in the cell becomes the measure of its vitality. If there has been excessive oxidation, or if the internal respiration of the cell has been minimized or prevented, then the normal acid-alkali balance between the nucleus and the cell body can no longer be differentiated by staining, that is, the cell has lost its difference in potential, which means that it has lost its power of function.

The loss of difference in potential in the cell may be due either to an excessive concentration of alkalis—alkalosis—or to an excessive concentration of acids—acidosis. The former state may be produced experimentally, but is rarely found clinically. Acidosis, on the other hand, is a common condition. It may be due to excessive oxidation, produced by excessive exertion, by fear, worry or anxiety, by trauma, by infection, by ether in the stage of excitation, by the injection of excessive doses of epinephrin, of strychnin, of iodin, by the ingestion of thyroid extract, by hyperthyroidism. That is, an excessive concentration of acids in the cell may result from the excessive production of acids as a result of any one or any combination of the excitants of metabolism. On the other hand, an excessive concentration of acids may result from the retention of acids in the cell as the result of diminished liver function, diminished kidney function, interference with pulmonary activity, or want of sufficient water.

The acid-alkali balance—potential—within the cell may be lost also as the result of a change in the

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permeability of the cell membranes. One of the common clinical causes of changes in the permeability of the cell membranes is ether anesthesia. In the first stages of ether anesthesia, the permeability of the cell membranes is increased, and excessive oxidation results, which is manifested by the stage of excitement. In this state, the rate of oxidation may even be trebled, causing an accumulation of acids within the cell, and consequent diminution of the difference in potential, with ultimate exhaustion. On the other hand, in deeper or surgical anesthesia, the effect is reversed; that is, the permeability of the cell membranes not only is not increased but is greatly diminished. Consequently, the cell is not only cut off from fresh supplies from without, but the escape of its own waste products is prevented. It follows that the internal respiration of the cells fails, and consequently the difference in potential between the nucleus and the cell body is rapidly lost, producing exhaustion, and ultimately death.

Ether is not the only anesthetic that may destroy the acid alkali balance—the difference of potential—of the cell. Deep nitrous oxid anesthesia also may materially lessen the difference in potential by lessening intracellular oxidation.

Finally, the most inclusive cause of the loss of difference in potential, hence of loss of cell energy, is loss of sleep, therefore the value of hypnotics, narcotics —bromids—opiates. Unbroken loss of sleep leads inevitably to death.

It follows that for the maintenance of its essential difference in potential the cell depends on (*a*) an abundance of fresh water; (*b*) oxygen; (*c*) rhythmic alternations of periods of rest and sleep.

These fundamental requirements are the final guide to the surgeon in his selection of conserving and remedial agents.

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VALUABLE AGENTS IN SURGICAL PRACTICE

To assure a sufficient supply of water and oxygen, it is essential to maintain an adequate circulation of blood bearing plenty of red cells, and to supply an abundance of fresh water. In cases of secondary anemia, therefore, a transfusion of blood is prescribed; and from 3,000 to 4,000 c.c. of water to which procain has been added to make a $\frac{1}{32}$ per cent. solution (Bartlett's method) is given subcutaneously every twenty-four hours. To assure that the supply of water and oxygen is carried to every cell with sufficient force and in sufficient volume, the heart muscle must be conserved and if necessary restored. To this end, if the impaired condition of the myocardium demands it, operation is preceded by the administration of the tincture of digitalis, 20 minims every four hours for fifteen doses. After operation, digitalin in $\frac{1}{25}$ grain doses is given hypodermically, every two hours for eight doses or until the tincture of digitalis can be given by mouth in the dosage and frequency noted above. This is continued until the desired effect is secured, unless nausea occurs, when it is discontinued at once.

In brief, therefore, to insure an adequate supply of fresh water and of oxygen to the cells, as may be required in the individual case, we utilize the transfusion of blood and the subcutaneous injection of water, both of which are driven through the organism with increased force and certainty as the result of digitalizing the myocardium.

Excessive activation by fear, worry or anxiety, with the resultant concentration of acids in the cells, is controlled by management, aided, when necessary, by bromids or by morphin; by using the readily taken, comparatively innocuous anesthetic, nitrous oxid oxygen; by administering the anesthetic in the patient's room and taking him to the operating room under anesthesia, and in selected cases, by the preoperative admin-

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istration of morphin and scopolamin for the purpose of maintaining an even metabolism, that is, an undisturbed internal respiration.

Excessive stimulation of the nerve cells by the trauma of the operation is controlled by local, regional or spinal anesthesia with procain—the safest local anesthetic for general use. Postoperative activation is controlled by the application of heat, by morphin, by blocking the traumatized area with quinin and urea hydrochlorid.

Atropin is used to prevent mucus, especially in operations on the respiratory tract. It is of especial value in laryngectomies, when it is used to prevent the reflex inhibition of the heart which may result from interference with the superior laryngeal nerves.

For the control of excessive metabolism as in postoperative hyperthyroidism, refrigeration by literally packing the patient in ice is specific. Bromids and morphin lessen the drive and aid in securing the state of negativity essential for restoring the difference in potential in the cells. In certain cases in which morphin acts as a stimulant rather than a narcotic, large doses of bromid given by rectum will quiet the patient.

Thyroid extract and thyroxin are used to supply the physiologic need in cases of thyroid deficiency; calcium lactate and parathyroid extract in cases of parathyroid deficiency.

Epinephrin is employed as an aid in the diagnosis of hyperthyroidism in borderline cases (Goetsch test). It is of value also in asthmatic attacks due to bronchial construction.

Magnesium sulphate is employed as a diagnostic aid in the detection of gallbladder disease or deficiency (Lyon test).

As we have indicated, oxygen, water, inhalation anesesetics, especially nitrous oxid oxygen, local anesthetics, especially procain, the bromids, morphin, scopolamin, atropin, thyroid product, and epinephrin have a definite value in surgical practice.

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In addition to these, it may be well to mention certain other agents which are rarely used and some of which are of doubtful value.

Alcohol and strychnin are rarely used. The former is of value in certain apathetic infections, especially in the aged or in those who have been accustomed to it. In general, with the exception of the employment of digitalis to stimulate a weak myocardium, the use of stimulants is scarcely worth while and may be harmful.

The use of a solution of sodium bicarbonate as an agent for combating shock is of little, if any, more value than water. In both war and civilian practice, it has been found that solutions of gum acacia not only have no value but probably have caused a number of deaths. Glucose solutions are of little value.

ANTISEPSIS AND ASEPSIS

The increasing tendency to consider as the final criterion of a therapeutic measure its value in protecting the working cells of the body against fatigue, as compared with older methods, may be compared to the contrast between antisepsis and asepsis, for the former importance of antiseptics has been largely replaced by the promotion of the natural defenses against infection which are present within the organism itself.

The surgeon today knows that the key to the defense against infection possessed by any part of the organism is its blood supply; that abundant blood and normal blood augmented by physiologic rest supply the natural "asepsis."

Nevertheless, certain antiseptic agents retain a valuable, if comparatively small, place in surgical therapy. Of these, the best is surgical solution of chlorinated soda (Carrel-Dakin solution). Beck's bismuth paste is useful, especially in the treatment of old sinuses. A 5 per cent. solution of picric acid in alcohol and tincture of iodin are about the best skin antiseptics.

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The tincture of iodin is useful also as an intra-uterine antiseptic application. Iodoform, despite its disagreeable qualities, still holds an important place as an inhibitor of infection. Surgical experience in the war taught us that contamination of raw tissue can be prevented or minimized (*a*) by preventing pooling of the wound secretions, and (*b*) by preventing the contact of contaminated with uncontaminated raw tissue. The latter requisite can be admirably assured by placing between the tissues a single layer of gauze lightly impregnated with iodoform. The application of this principle has proved of especial value in resections of the rectum and of the large intestine for cancer.

Much might be added regarding many other admirable agents of value for the irrigation of cavities, cleansing the skin, and so forth, but the relative value of any of these as compared with methods which utilize the natural defenses and reparative forces of the patient may be summed up in the subjoined excerpt from a previous paper

> Good surgery is the exponent of no single method. It recognizes the anatomical and environmental situations in which chemical and physical agencies are useful. Good surgery exploits physiologic rest and fluids and sleep; it gives little pain. Good surgery evokes confidence; and confidence begets rest; and rest begets restoration. Good surgery, then, makes use of antiseptics and physical forces, just as it uses incisions, counter-drainage, revisions, skin-grafting, blood-transfusion. Good surgery does not substitute an easy formula for its principles; above all, it always is dissatisfied with its work and always is open to suggestion.

Anociation and asepsis leave but little place for the heroic medication of the past.

RESULTS AT LAKESIDE HOSPITAL

By the extension of employment of anociation and asepsis, the mortality in the last 6,261 operations at Ladkeside Hospital has been reduced to 1.6 per cent. Our series have included fifty-eight colostomies and resections of the rectum and large intestine for cancer,

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with one death, and seventy resections of the stomach and gastro-enterostomies for cancer and ulcer of the stomach, with one death. Anociation and asepsis have made possible a series of 227 consecutive thyroidectomies and 180 consecutive ligations, that is, 407 consecutive thyroid operations for hyperthyroidism without a death. These are not selected cases. No patient was rejected and many were dying. Among the last 500 thyroidectomies, there have been five deaths, a mortality rate of 1 per cent., among the last 500 ligations, two deaths.

Worth while medication in surgery is that which is based on the principle of conservation and restoration of the cells, as interpreted by modern conceptions of the laws that govern the human organism.

Euclid Avenue and Ninety-Third Street.

ABSTRACT OF DISCUSSION

DR. JOHN J. GILBRIDE, Philadelphia: A recent paper on goiter by Dr. Crile emphasized how important it is for the surgeon to be competent to manage his own cases, for all surgeons are not so fortunate as to have skilled assistants, such as biochemists, physiologists and others, always available. It would be very laudable, of course, and most desirable, for those of us who could, to have associated with us capable men to handle such phases of the subject. However, there is no one who is in a better position to know and who should recognize the onset of menacing symptoms better than the surgeon and consequently treat these patients early.

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THE USE OF DRUGS IN INFANCY AND CHILDHOOD*

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ROCHESTER, MINN.

In times past, many have considered pediatrics nothing more than the practice of internal medicine, with a formula for the reduction of the dosage of drugs. Within the last twenty-five years, however, there has been a tremendous development in this branch of medicine. A visible manifestation of this development is the establishment of special chairs in universities, both in this country and abroad. Perhaps the most important development of the intensive work in pediatrics has been in the realm of preventive medicine; drug therapy has not kept pace with the progress in other fields of this specialty. The interest which the profession at large has taken in pediatrics is perhaps best illustrated by the establishment of local and regional pediatric societies.

The literature of the last few years on drug therapy in infants and children indicates the slight effort that has been made in recent years in the development of such therapy. The lack of interest in this work during the rapid expansion of pediatrics in general is therefore evident.

RELATIVE DOSAGE

The main point in the administration of drugs to infants and children still is the reduction of the adult's dose. Drug therapy in infants and children, therefore, not only shares all the faults it has in the adult, but since the various formulas for calculating the dosage

* From the Section on Pediatrics, Mayo Clinic.

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are based on weight or on age, or on weight and age, a specific error is introduced, for the child is not a pocket edition of the adult, and the two cannot be compared pound by pound. During growth, the relationship of the various organ-systems of the body to one another shifts, and with this process, the relationship of each organ-system to the whole body shifts. For instance, in the new-born infant about 23 per cent. of the total weight is in the muscles; in the adult about 43 per cent. is in the muscles. The relative weight of the infant's liver is about two and one-half times greater than that of the adult. This is of great importance, for a number of drugs do not distribute themselves equally over the body, but have certain affinities for various tissues or constituents of tissue. The affinity of many narcotics for lipoid tissue is well known. Some further factors enter into consideration. The administration of chloroform to an adult dog readily produces necrosis of the liver, but the production of this necrosis of the liver is far more difficult in the pup, where the relative large amount of glycogen exercises a protective influence.

It is stated that certain drugs are well tolerated by the infant, while others are not. This statement also rests on a comparison with dosages for adults, and emphasizes the necessity of a study of the pharmacologic action of various drugs in the infant. The functional activity of some organs develops in the course of growth, like that of the sexual glands. Their internal secretions exercise an influence on the organism, and, while it is a fact that we know the chemistry of the secretions of only two glands, suprarenal and the thyroid glands, we must assume that the activity of the secretions of other glands also depends on one or more chemically well defined substances. These substances, whatever their derivation, may have a decisive influence on the reaction of the organism to drugs. In this connection, the results of Le Heux,

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from the laboratory of Magnus,[1] are of the greatest importance. They confirm the theory that the sodium salts of acetic acid and pyruvic acid increase the stimulation of the isolated intestine, and supply strong evidence to indicate that this stimulation is due to the formation of ester of acetic acid and pyruvic acid with the cholin normally present in the intestinal walls.

These factors are sufficient to prove that the administration of drugs to infants by formula is very unsatisfactory, and depends entirely on chance. Drug therapy in the infant has suffered, like that in the adult, from a number of mistakes and fallacies. First, only a small number of drugs exercise a rapid and striking effect, either by destroying the main causative agent of a disease or by producing a lasting favorable effect on it. Second, there is therapeutic nihilism, which is both fashionable and convenient; some of its roots strike deep into the quagmire of muddled observations. It is a remarkable phenomenon in the history of medicine that even the keenest observers lose their power of criticism and judgment when discussing therapy. Third, carefully controlled studies of the action of drugs in the infant and in the child exist, if at all, only in limited numbers.

DRUG GROUPS

In order to establish a standardized list of drugs essential to the treatment of the diseases of infancy and childhood, I selected from the pharmacopeia a list of sixty-one drugs. This list I sent to eighty-four men who are limiting their practice to pediatrics, with the request that they check the drugs listed and add to them any drugs which they considered essential in their practice. Of the eighty-four men, sixty-four responded. I wish to thank these gentlemen for giving me the benefit of their experience. A short analysis of the responses is of interest.

1. Magnus, R.: Cholin als Hormon der Darmbewegung, Die Naturwissenschaften, 1920, No. 20, from a lecture held Feb. 2, 1920, in Bataafsch Genootschap voor proefondervindelyke sysbegeerte, at Rotterdam.

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LIST OF DRUGS SUBMITTED TO PEDIATRICIANS

		Recommendations	
1.	Silver		63
	Nitrate	48	
	Argyrol	58	
2.	Mercury		64
	Blue ointment	52	
	Calomel	50	
	Ammoniated mercury	55	
	Mercuric chlorid	39	
3.	Arsenic		61
	Fowler's solution	49	
	Sodium cacodylate	24	
	Arsphenamin	50	
4.	Iron		60
	Syrup of ferric iodid	51	
	Blaud's pills	35	
	Ferric citrate	40	
5.	Phosphorus	42	
6.	Cod liver oil	63	
7.	Iodin		50
	Potassium iodid	43	
8.	Turpentine	17	
9.	Mustard	49	
	ANTISPASMODICS		
10.	Epinephrin	53	
11.	Atropin	58	
	Belladonna	43	
12.	Magnesium sulphate	36	
13.	Calcium chlorid	49	
	STIMULANTS (HEART AND CIRCULATORY SYSTEM)		
14.	Camphor	52	
15.	Digitalis	62	
16.	Strophanthus	25	
17.	Nitrites	20	
	RESPIRATION (CENTRAL)		
18.	Strychnin (tincture of nux vomica)	40	
19.	Caffein	50	
	HYPNOTICS		
20.	Alcohol	28	
21.	Chloral hydrate	55	
22.	Barbital	17	
23.	Luminal	36	
24.	Bromids	61	
	LOCAL ANESTHETICS		
25.	Procain	47	
26.	Ethyl chlorid	30	
27.	Orthoform	13	
	LAXATIVES		
28.	Castor oil	55	
29.	Senna	26	
30.	Rhubarb	32	
31.	Jalap	12	
*32.	Aloin	3	
33.	Cascara sagrada	55	
34.	White liquid petrolatum	45	
35.	Sodium sulphate	45	
	ASTRINGENTS		
36.	Tannates	25	
37.	Bismuth	51	
	Opium series		62
38.	Opium	30	
	Morphin sulphate	46	
	Paregoric	47	
39.	Codein sulphate	54	
40.	Heroin	20	

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RESPIRATORY TRACT

41.	Ipecac	48
42.	Ammonium carbonate	33
43.	Squills	14

ANTIPYRETICS

44.	Quinin	48
45.	Antipyrin	49
46.	Phenacetin	36
47.	Pyramidon	13
48.	Acetyesalicylic acid	52
49.	Sodium salicylate	49

ANTHELMINTICS

50.	Male fern	62
51.	Santonin	64

DIURETICS

52.	Citrates	53
53.	Acetates	34
54.	Theobromin sodium salicylate	25

ALKALIS

55.	Sodium bicarbonate	62

URINARY ANTISEPTICS

56.	Hexamethylenamin	59
57.	Salol	30

MISCELLANEOUS

58.	Menthol	36
59.	Phenol	45
60.	Sulphur	44
61.	Boric acid	56

Many of the drugs were grouped under special headings, such as antispasmodics, laxatives, cardiac stimulants, and antipyretics. Only mercury in some form and santonin, on the list submitted, are used by all sixty-four men. Besides these, silver, arsenic, iron, sodium bicarbonate, cod liver oil, and at least one representative of the opium series, the antispasmodics, heart and circulatory stimulants, hypnotics, laxatives, antipyretics, anthelmintics, and urinary antiseptics, were used by sixty men of the sixty-four. One half of the men used forty-three of the drugs indicated on the list.

A number of men added drugs to the list. Fourteen added milk of magnesia, and three or more added benzyl benzoate, hyoscyamin, chloroform, agar-agar, creosote, chenopodium, glycerin, and tincture benzoin compound. One man added thirty-eight drugs to the list.

The drugs in this list can be readily divided into four groups. The drugs in the first group have specific

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indications; for example, mercury, arsenic, quinin, santonin, male fern, etc., act directly in destroying parasites, and the drugs such as silver, hexamethylenamin and the salicylates, have definite antiseptic powers for destroying bacteria. The indication for the use of these drugs is usually given with the diagnosis of the disease. The drugs in the second group regulate the function of the different organs; for example, digitalis, the group of laxatives, and the diuretics. The third group is essentially for the symptomatic treatment of disease, as morphin for the relief of pain. The fourth group consists of drugs that are used for a specific purpose, and for practically no other, such as phosphorus in the treatment of rickets and spasmophilia, mustard for counterirritation, and phenol (carbolic acid) for the infections of the middle ear. This classification does not differ greatly from the old pharmacopeial classification of drugs which rested on the *indicatio vitalis, causalis, morbi* and *symptomatica.*

It is not my object here to attempt an enumeration of the indications for the use of these various drugs. I merely wished to collect a group of drugs that, in the experience of a large number of pediatricians, cover the needs in the practice of pediatrics.

INDICATIONS FOR DRUG THERAPY

The importance of a definite indication for the use of drugs is even more essential in infants and children than it is in adults. As Dr. Jacobi has said, "Most conditions in childhood right themselves without any medication," and, "I believe we are justified in assuming that the man in general practice uses more medicine, rather than too little, for the welfare of his little patients."

The tendency toward homeopathy, particularly in the treatment of diseases of children, so much in vogue about thirty-five years ago, when adults were treated by regular physicians and children by homeopathic

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physicians, was the logical outgrowth of too much medication. Today the homeopathist, the indications for drug therapy being much more finely drawn, has almost disappeared from our midst. The public, too, has become educated, so that, as a rule, it appreciates the advice given by the physician more than the prescription he writes.

In infancy, in particular, the use of drugs should be limited to definite indications, and these indications are usually for a single drug. The younger the child, the greater the danger of upsetting its gastro-intestinal functions by medication. Diseases of the infant, of whatever nature, frequently manifest themselves by gastro-intestinal symptoms. Indeed, in many cases they are the only symptoms, and it is very important not to derange the gastro-intestinal tract still more. The treatment of parenteral infections by repeated catharsis is perhaps the best example of the danger of treatment without a diagnosis.

PROBLEMS OF ADMINISTRATION AND DOSAGE

It has been the general experience that the difficulties of administering medicine are not so much those of giving certain medicines to children, as those of giving any medicines to certain children. In this connection two very important points must be emphasized: first, it is usually children who are unwilling to cooperate who are unwilling to take medicine, another example of the spoiled child; and, second, the physician fails to appreciate the importance of his personal relationship with his little patient. The fact that a child promises to take the medicine is very much better than any assurance on the part of the mother or nurse to administer it.

We are not limited, in our administration of medicine, to the oral route, but, as it is by far the simplest method, it is most frequently used. When a child, either because of mood or as the result of illness, is

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unwilling to take medicine by mouth, it can very easily be given with a nasal tube. The rectum, too, can be used as a means of administering drugs, particularly the drugs, such as chloral hydrate, that are likely to irritate the stomach.

The dose of chloral hydrate by rectum as usually given is about twice the dose by mouth. Intravenous injection insures quicker action with a smaller dosage. It must be remembered, however, that, for a drug to develop its pharmacologic action it must be in contact in sufficient concentration with the tissues to be acted on, for a definite length of time. This means, the more rapid the absorption, the lower the dose, but, on the other hand, the shorter the action, the greater is the necessity for repetition of the dose, for constant action. Another factor to be considered in this connection is the rapidity of elimination, as shown by Ramsey's and Groebner's [2] work with mercury.

The treatment by drugs of diseases in infancy is influenced in its effectiveness by the factor of nutrition and growth. This is perhaps best expressed by the statement that as long as a child eats and digests well there is a good chance for recovery. A drug which acts favorably on the disease focus but interferes with the nutrition of the child is harmful. The effect of the so-called tonic treatment during the active stage of disease is another example of the failure to recognize the nutritional factor in disease.

I shall call attention also to the necessity of objective standards for the value of drug therapy. At present almost all our judgment is subjective, and the results of drug therapy depend to a large degree on whether the physician is an optimist or a pessimist. Until we have objective standards, the relative values of various modes of treatment must, of necessity, be

2. Ramsey, W. R., and Groebner, O. A.: Further Progress in the Study of the Relative Efficiency of the Different Mercurial Preparations in the Treatment of Congenital Syphilis in Infants and Children as Determined by a Quantitative Analysis of the Mercury Elimination in the Urine, Am. J. Dis. Child. **20**: 199 (Sept.) 1920.

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difficult to determine. It behooves us all, therefore, to apply objective measurements, wherever possible, in our studies of drug therapy.

My original plan was to include in this paper a table of the doses of drugs for the different age periods. On second thought, however, it seemed too important a matter to be decided arbitrarily by the opinion of any one physician; such a table, dependent as it is on experience rather than experiment, is a problem that calls for cooperative effort. I was strengthened in this belief by looking over Lavialle's tables on the dosage of drugs for the first two years, which appeared in Variot's recent textbook.[3] He designates a dose for the first month; for older infants he multiplies the dose by the number of months the child is of age, merely another mode of dosage according to age, without any consideration of the peculiarities of infancy and childhood.

In concluding I wish to propose that the Section on Pharmacology and Therapeutics recommend to the proper authorities the appointment of a committee for the purpose of studying the problem of the therapeutic action of drugs and their dosage in infancy and childhood.

ABSTRACT OF DISCUSSION

Dr. F. Paul Gengenbach, Denver: When we realize what a large proportion of the acute illness of early childhood are due to disturbances in the gastro-intestinal tract, we might say that the first thing for a sick child is not to give it any drugs or any food. Push the water drinking. Let water be the therapeutic agent. Then after you learn just what the nature of the disturbance is, start feeding, gradually increasing the amount to the point of tolerance. Nutrition is the important thing, It is very important not to upset digestion. We can use drugs in different ways. We can use what might be termed an average dose, at average intervals. That is, so much of a drug every two, three or four hours, estimating the dosage by Young's or some other rule. On the other hand, there is something to be said in favor of what might be termed homeopathic dosage. I find frequent

3. Variot, G.: La puériculture pratique, ou, l'art d'eléver les enfants du premier age, Paris, Doin, 1912.

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use for fractional dosage. I use it in all children that I am seeing for the first time, because I know nothing about their idiosyncrasies or their reactions. In the second place, I use it in consultation practice, because I feel it is safer to prescribe in that way, for the practitioner is going to superintend the case after I leave. And, thirdly, I use fractional doses at frequent intervals when I am anxious to get plenty of water into the child. Another factor is palatability. It is something to prescribe a drug, and something to get it down. Another important phase is to give drugs so that they do not upset digestion. In a general way, since the child has a good chance of getting well without medication, it would be safer to look after the child's nutrition and not give any drugs. However, it ought to be possible to do both. In addition to food and drug therapy, the other things we always think of in pediatric practice are mechanotherapy and hydrotherapy, including steam inhalations and counter-irritation and all kinds of baths. I want to second Dr. Helmholz' suggestion that this section appoint some sort of committee or commission, consisting of pharmacologists, therapeutists and pediatricians, so that this matter may be gone into in a scientific manner, and so that we will have something definite to give to the general practitioner, who, after all, treats the majority of children.

Dr. Richard M. Smith, Boston: Children tend, on the whole, to get well. Children have very little chronic disease or very little disease which is evidenced by degeneration of one form or another. We must, in general, consider conditions which represent temporary derivation from a normal healthy condition to which the patient tends to return. Largely, I think, because of this fact, pediatricians and general practitioners dealing with children have become less and less accustomed to the use of drugs. In doing this we have suffered because we have failed frequently to avail ourselves of drugs which are of real value. Therefore, I think Dr. Helmholz' plea is particularly timely, that we shall familiarize ourselves again with the facts we already know with reference to drug therapy as applied to children, and we shall also attempt to increase our knowledge, particularly with reference to the dosage that it is necessary to give to produce satisfactory results. We frequently give up the use of certain drugs because unable to produce satisfactory results, and these results are unsatisfactory because we have used the drug inaccurately, or because we have given a dose which is insufficient to produce the desired results. We should confine ourselves, for the most part, to the use of single drugs, and should familiarize ourselves with those drugs so that we shall actually know when to employ them, and then learn the dosage of these drugs so that we may employ them intelligently.

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DR. J. I. DURAND, Seattle: In regard to starvation: If there is an infection ouside the intestinal tract, we are not justified in starving the child. Keeping up the child's nutrition is a very important factor in effecting a cure. If the infection is outside the intestinal tract, and if the child is hungry and wants food, it is safe to feed the child a soft diet. That does not necessarily mean a liquid diet. Gruels and vegetables are taken care of just as well as milk. The younger the child, the more danger there is of starvation ,and infinite damage has been done to a tiny baby by the barley water feeding continued over a long period. It is never justified. Starving a baby under 6 months for more than twenty-four hours is never justified. Another practical point in the treatment of children is that too many laxatives have been used. Calomel should not be given to a child under 3 years old. It is a drastic purge, and does much damage. Phosphorus and cod liver oil are specifies in rickets. I use 1 c.c. oil of phosphorus to 100 c.c. of cod liver oil, in rapidly increasing doses up to 2 or 3 drams daily. Chloral is a very valuable drug in infancy, especially in convulsions, and can be given in relatively large doses, 2 grains by mouth, or 4 or 5 grains by rectum, in repeated doses, to a child 1 year old. Pyelitis is extremely common. You can give large doses of hexamethylenamin if you do not continue more than twenty-four hours. Two grains for a baby of 6 or 8 months old or even 1 year old, every two hours for twenty-four hours, has never caused damage. Then stop and alkalize the urine with potasium citrate, because the infection is usually due to the colon bacillus, which will not grow in an alkaline solution. Keep this up five days and repeat the hexamethylenamin.

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THE VALUE OF DRUGS IN OPHTHALMOLOGY

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Previous speakers have given us the general principles of pharmacotherapy. Therefore, in discussing the use of drugs in eye affections it is the practical applications of those principles to individual remedies in ophthalmology that should be considered.

In discussing the use of drugs in the treatment of affections of the eyes, the great assistance of heat, cold, electricity, massage, roentgen ray, radium, organ therapy, the serums, surgery and, occasionally, even bleeding, must be borne in mind. Space does not allow even the mention of all the drugs that are useful in ophthalmology, so that I will discuss principally those remedies which have in my own experience proved valuable.

The late Dr. Reber very truly noted the fact that the laboratory tests for the efficiency of drugs vary so much in their biologic surroundings from the clinical tests that exact coincidence cannot be expected. He said:

> And if perchance there should be a conflict in testimony between the test tube in the laboratory and the results of carefully conducted therapeutic tests in the consulting room or clinic, my voice would be raised in favor of the latter until such a time as the results can be harmonized.

DRUGS ADMINISTERED INTERNALLY FOR EYE AFFECTIONS

Salicylates.—These are of proved value in certain inflammations of the uveal tract, especially in sympathetic ophthalmia. They lessen pain, promote rest and sleep, and directly affect the local inflammatory process.

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Sodium salicylate is the best of these representatives of the virtues of salicylic acid. In sympathetic ophthalmia, best results have been obtained by very large doses.

Acetylsalicylic acid ("aspirin") is less disturbing to the digestion, and at the same time it is more prompt in its analgesic effect. In inflammatory conditions and discomfort following eye operations, 10 grains of acetylsalicylic acid given at bedtime will often assure a good night's rest and help to hasten recovery. This means a great deal when restlessness or anxiety is a real handicap to convalescence.

Iodids.—Potassium iodid and sodium iodid were the sheet anchors of our ophthalmologic fathers. While they do not destroy the spirochetes in syphilitic conditions, they do cause the formation of a protolytic ferment that has a distinctly selective action on the cellular elements of new tissue growths, or on inflammatory exudates. They therefore deserve to hold their place in present day therapeutics in both syphilitic and nonsyphilitic eye affections. In interstitial keratitis associated with congenial syphilis, the iodids have proved themselves of real value. This is also true in extensive choroidal lesions with vitreous opacities, irrespective of the cause. In gumma of the iris or ciliary body, I have observed the growth to disappear very rapidly under the internal administration of rapidly increasing doses of potassium iodid. Its effect on the formation of new cell growth is well illustrated in melanosarcoma of the choroid when unintelligent patients have for a time refused enucleation of the eye. In such cases I have seen the tumor grow less and the sight improve. Unfortunately, the tumors have shown a fulminating growth with the cessation of the iodids. Owing to the effect of the iodids on exudates in the interior of the blood vessels, they are of value in arteriosclerotic processes involving the choroid, retina and optic nerve. In older people, when the drug has

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been given over a long period of time, sodium iodid and strontium possess advantages.

Syrup of ferrous iodid is of much value in many ocular conditions, especially those occurring in cases with poor nutrition. In writing about this medicine, Dr. Reber said:: "In the interstitial keratitis of children, it is almost a panacea."

Bromids.—The bromids of sodium or potassium assist ophthalmic surgery by their sedative action on the nervous system, the depressing effect on the motor area of the cortex, and by allaying reflex excitability. In nervous people with poor control, the use before an operation of bromid in addition to the application of local anesthetics will prevent the danger of "squeezing," and will assist the patient in maintaining the necessary quiet after the operation.

Nitrites.—The action of sodium nitrite is similar to that of the other members of the nitrite group in producing vasodilatation and reducing blood pressure. It is useful in retinal hemorrhages in older people when there is high blood pressure.

Amyl nitrite by inhalation is helpful in making a diagnosis in cases of toxic amblyopia. It also has a therapeutic value in the later stages of those cases in which there is a paleness of the temporal portion of the nerve.

Nitroglycerin has been used in cases of embolism of the central retinal artery. But my experience with this and other drugs in such cases has not been satisfactory.

Calcium Salts.—Calcium lactate seems to possess a definite value when given in the dose of 5 grains three times a day for several days preceding an operation on the iris or muscles whenever the patient's coagulation time is markedly slow. In those cases in which there are recurrent hemorrhages of the retina, it is a valuable addition to the other appropriate remedies.

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Barbital ("veronal").—This is usually very effective in producing sleep after operation, but sometimes produces great excitement instead. To use a patient's expression, "It set me nearly crazy." Its use, therefore, in ophthalmic surgery is not without some danger.

Cathartics.—Properly employed, these are of much value in ophthalmic practice. Of these, casara sagrada is especially valuable on account of its effect on the colon.

Cinchophen ("atophan").—This possesses the power of hastening the elimination of uric acid and the urates. In cases of increased blood-uric acid and a general so-called gouty tendency, cinchophen administered in 5 grain doses three times a day, before an intra-ocular operation, tends to diminish the danger of a postoperative iritis or iridocyclitis. It is very effective if given later in these cases when these conditions actually arise after an operation.

In hysterical patients, when the hysterical condition is complicating recovery, asafetida or valerian will have a quieting and, therefore, beneficial effect. I am not prepared to say whether the effect produced is carminitive, or whether it is purely mental from the evil odor and taste.

Hydrochloric Acid, Dilute.—This is valuable when there are vitreous opacities without any visible fundus lesion, and which seem to be connected with a gastro-intestinal toxemia. Its stimulating effect on the stomach secretions, and its antiseptic effect on the intestinal tract, have been frequently mentioned.

Strychnin.—The salts of strychnin can be used to advantage in cases of paresis of ocular muscles (including that of accommodation after diphtheria). They are also useful in cases of partial optic atrophy, in the later stages of toxic amblyopia, and in weakness of accommodation and convergence in neurasthenic conditions. It is well to remember the cumulative effect pointed out by Hare and others. It is best given hypo-

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dermically, and has to be pushed until toxic effects are shown in order to get the best results.

Hexamethylanamin.—This product of ammonia and formaldehyd is often useful to the ophthalmic patient after operations whenever bladder complications cause much trouble and restlessness from constant desire to pass the urine.

Opium.—Morphin sulphate has an analgesic, relaxing and depressing effect on the whole central nervous system. It is very valuable before operations on very nervous and pain-sensitive persons. It relieves the dread and the nervous shock of the operation, enables the patient to hold still without "squeezing," and enhances the effect of the local anesthetic. Before cataract extractions, it can be given in combination with atropin; in glaucoma, in conjunction with strychnin. It should, however, never be given before an operation unless the effects on that individual patient have been ascertained beforehand, because in some people morphin causes great cerebral excitement, nausea and vomiting.

Codein is not as subject to individual idiosyncrasies as morphin, so that it can often be substituted with advantage for morphin. It is an effective reducer of pain, a good hypnotic and sedative. It is very useful in reducing cough or pain in operative cases.

Arsenic.—Liquor potasii arsenitis (Fowler's solution) is very useful in some cases of clonic blepharospasm and also in later stages of malarial keratitis.

Arsphenamin.—Given intravenously, this has proved of great value in all stages of syphilitic eye lesions. Just as in cases of syphilitic manifestations in other parts of the body, so in the later phases of the disease in the eye, it is well to associate arsphenamin with mercurials. My experience with intraspinal medication in syphilitic optic nerve lesions has not been very extensive. But so far, I have seen personally only one case in which the sight suddenly lessened after the

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first injection. Several cases have been seen in which the atrophic condition was helped and the improvement has been maintained. Other cases have been seen in which the optic atrophy continued its usual sad course, uninfluenced by the injections.

Neo-arsphenamin has not shown any great advantage over the first named arsenic preparation.

Mercurials.—In spite of the introduction of arsphenamin and other arsenic preparations, mercury still has a place in modern ophthalmologic therapeutics. Dr. Reber speaks of calomel as "that gift of the gods." In addition to its general effects, it is very valuable in all inflammatory eye conditions, in unloading the intestinal tract of toxic material. Even people who are much annoyed by "muscae" affirm that the specks are much less troublesome "after a good cleaning out with calomel." In syphilitic conditions, the internal, the intramuscular injection, and the epidermal administration of mercurial preparations are very valuable. In ocular manifestations of congenital syphilis in children, it is of great value given as suggested by Fordyce and Rosen. The administration of mercuric chlorid in conjunction with injections of neo-arsphenamin has been very effective.

Pilocarpin.—The general effect of pilocarpin by mouth and by hypodermic application have been so often described that it is not necessary to add anything more than the statement that I still have faith in its virtue when properly applied in selected cases of uveal inflammation and inflammation of other ocular tissues.

LOCAL ANESTHETICS OR ANALGESICS

One of the grea epochs in ophthalmology opened in 1884 when Karl Koller discovered the anesthetic properties of cocain, for it was through his powers of observation that this precious boon was given to suffering humanity. Surgeons and patients the world over should rise up to call his name blessed.

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Cocain hydrochlorid, owing to its free solubility, has been the form in which cocain has been generally used. This salt—the oldest of the family of local anesthetics—though supplanted by many synthetic products, under some conditions, still has a niche which it fills effectively. In addition to holocain for ocular operations, with atropin in certain severe inflammations of the uveal tract, and with miotics in painful cases of absolute glaucoma, cocain has no rival. But on account of its instability, toxicity, dilating effect on the pupils, drying effect on the corneal epithelium, and its danger of causing glaucoma, it is best supplanted in certain cases by some of the newer products of synthetic chemistry.

The principal synthetic products are beta-eucain, holocain hydrochlorid, stovain, alypin and procain.

Holocain is used chiefly because of its antiseptic properties, absence of effect on the pupils and corneal epithelium, and lesser toxicity. For use in office work for removal of foreign bodies on the cornea, etc., its advantages are obvious. Its sterilizing and stimulating effect on corneal ulcers makes it doubly valuable. In major operations I have instilled in the patient's eye a 1 per cent. solution of fresh holocain hydrochlorid every five minutes for twenty minutes before the patient comes to the operating room.

The subconjunctival injection of a 0.5 per cent. solution of procain with epinephrin in addition to the local instillation has been very efficacious in intra-ocular operations. Generally the injections are given below; but in sclerocorneal trephining, in muscle operations, and in some cases of iridectomy, the injections are made at the site of the operation. Even in cases of glaucoma, epinephrin is added to the procain. In glaucoma cases that are suitable, a hypodermic of morphin with strychnin is also given twenty minutes before the operation.

Ethylmorphin hydrochlorid ("dionin") acts as an analgesic and as a local vasodilator. I use it for its

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absorbent effect in postinflammatory and postoperative conditions. In corneal scars uveal exudates and vitreous opacities it seems to assist Nature in bringing about absorption. It is well to remember the varying individual sensitiveness to this drug. Some persons stand an initial strength of 1 per cent., while others experience great discomfort from one-fifth that strength. The patient should be informed beforehand of the local effects it is likely to produce, especially the reflex sneezing. I use at bedtime the weakest solution possible to obtain the vasodilatory effect.

CYCLOPLEGICS AND MYDRIATICS

Atropin is the historical progenitor of this group of drugs. Murray quotes Fukala as stating that belladonna was first introduced between 500 B. C. and 130 A. D. Owing to Galen's disfavor, its use was abandoned for many centuries.

The great value of atropin sulphate in ophthalmic therapeutics is too well recognized to require mention. Without it (or some of its substitutes) the present day ophthalmologists would indeed be lost. However, it is a potent drug and should at all times be used with care. In all elderly people, or in young people with a glaucomatous tendency, its use should be confined to those cases in which no substitute would answer the purpose. In all cases in which cycloplegics are used for purposes of refraction or ophthalmoscopic examination, a 1 per cent solution of pilocarpin should follow the completion of the test. Children are especially sensitive to atropin, and there are few of us who have not seen the flushed face, dry mouth, bright eyes, rapid pulse and respiration, and great excitability following its use. Some very asthenic persons exhibit a marked idiosyncrasy for it. I have seen mydriasis and partial paralysis of accommodation lasting several days from a belladonna plaster placed on the back. It is also felt that the long continued use of cathartics containing belladonna, in

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the cases of elderly people, may in a few instances play a contributing part in the causation of chronic glaucoma. Locally, at times, it causes a conjunctival irritation resembling trachoma. Even a local dermatitis follows its use. This disturbance disappears quickly after the atropin is discontinued, and the appropriate remedies used. Owing to its toxic action, many substitutes are used in ophthalmic practice, though in inflammatory lesions of the uveal tract it still holds first place. When the patient exhibits an idiosyncrasy for atropin, I have found for therapeutic purposes that scopolamin hydrobromid is the best substitute. This is especially true in operative cases for glaucoma, and in those cases in elderly people when atropin has an exciting action. It has less tendency to cause local irritation, or to increase tension, and acts as a cerebral sedative. However, it must not be used in strong solution, for some people are easily affected by it. For purposes of testing the static refraction in cases in which atropin is not advisable, I prefer a 1 per cent solution of homatropin hydrobromid to which one drop of a 4 per cent solution of cocain is added to one dram of the solution. This addition does away with the local irritation of the homatropin, but is not strong enough to interfere with the corneal epithelium. The homatropin is instilled every fifteen minutes for two hours for purposes of testing the refraction. The recent retesting of cases in which this method was used twenty-five years ago makes one feel that, on the whole, the results have been satisfactory.

For the ordinary case of ophthalmoscopic examination, I have found that euphthalmin (which is now being manufactured under the name of "eucatropin") is the drug *par excellence*.. Its use also is made more satisfactory by the addition of a very minute amount of cocain. One instillation in persons over 50 years of age usually gives marked mydriasis in from thirty to thirty-five minutes. In very elderly people, the

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instillation of a 4 per cent solution of cocain repeated at the end of ten minutes usually gives a satisfactory dilatation of the pupils at the end of fifteen minutes from the first instillation. It is most important in all cases in which cocain is used to keep the eyes closed as much as possible until the examination is made in order to prevent the irregularity of the corneal epithelium. Some observers have reported satisfactory results from the use of duboisin and daturin.

LOCAL ANTISEPTICS AND ASTRINGENTS

The ophthalmologist as well as the patient must regard boric acid with a sense of eternal gratitude. Though it has been in use for more than 200 years, it still holds the place of regard. It is most widely used as a household remedy, a standby in ophthalmic practice, and a constituent of nearly all proprietary collyria. Its safety and its soothing qualities warrant the continuation of its use.

Mercuric chlorid has long stood at the head of the list of antiseptics in ophthalmic practice. It is of great value in irrigating the conjunctival culdesac in a 1 : 5,000 or 1 : 10,000 solution before the operations. In the shape of a salve of 1 : 5,000, it can be used in the bandaged eye the night before an operation and for filling the eye after an operation. In cases of corneal ulcers, the salve is very efficacious when used in the eye every two hours, in addition to the other treatment. In a few cases, when an idiosyncrasy exists, it causes conjunctival irritation, chemosis and dermatitis. The patient should be tested before the operation for the possibility of such an idiosyncrasy.

Some operators of great experience prefer mercuric oxycyanid.

Chlorin water is one of the most satisfying of all antiseptics in the treatment of certain types of blepharitis, especially blepharitis squamosa. The official chlorin water is used in the strength of one dram to

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half a pint of tepid water, and the lid margins are thoroughly washed twice a day with absorbent cotton.

Solution of formaldehyd is very valuable in the treatment of corneal ulcers. It may be used by direct application to the anesthetized ulcer in the strength of 1 : 50, on a cotton tipped probe, or it may be used as an irrigant in from 1 : 1,000 to a 1 : 5,000 solution.

Iodin is very efficacious in the treatment of corneal ulcers. A 2 per cent solution applied to the lid margins is a remedy that has no superior in nearly all cases of blepharitis. Of course, it is essential that all crusts should be removed first.

Yellow mercuric oxid with good reason is a favorite remedy in all inflammation of the lid margins. However, in some cases it acts as a marked irritant, causing a toxic dermatitis. In these cases, ichthyol as a salve is a good substitute, as the most sensitive skins do not seem to resent its presence.

Resorcin, too, alone or in combination with other drugs such as oxid of zinc ointment, is very efficacious.

Among the newer remedies, ethylhydrocuprein hydrochlorid ("optochin"), a quinin derivative, is particularly effective in any pneumococcus affection of the eye or eyelids. It is very valuable in serpiginous ulcers, in all forms of purulent conjunctivitis, and in blepharitis. In the case of the last, I use it in a 2 per cent solution, while in the former cases I use it in a 1 per cent solution. The solution should be fresh.

A still more recent antiseptic is mercurochrome, which is a combination of fluorescein and mercury. It is very highly thought of by Dr. Lancaster and his colleagues on account of its germicidal, nonirritating, yet penetrating qualities. Dr. Lancaster advises its use before operations, and also in acute infections of the ocular and palpebral conjunctiva. It may be used in strength from 1 to 2 per cent solution.

Pyoktanin (one of the anilin dyes) has been much lauded as a remedy for various eye infections, but I

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have not found it to possess as satisfactory antiseptic properties as some of those already mentioned.

Silver nitrate has long been recognized for its valuable antiseptic and astringent effects in diseases of the conjunctiva. Its effectiveness in gonorrheal conjunctivitis in the adult and in the new-born cannot be denied. Its application, however, is painful. As a preventive measure in the new-born its use is not without danger when in a 2 per cent solution it is dropped on the delicate cornea. I have seen several cases in which its use was followed by great reaction and whitening of the corneal epithelium—with much alarm to the physician and parents. Owing to the irritating effect of silver nitrate, many substitutes have been found in the silver protein compounds. Among the many, argyrol has proved of great value from its germicidal, cleansing, yet non-irritating qualities. In spite of early laboratory tests showing the inertness of argyrol as a bactericide, ophthalmologists of the greatest clinical experience have continued to report satisfactory results from its use in a multitude of different cases. Later laboratory tests have corroborated the clinical findings of its effectiveness. One of its foremost champions is Dr. Bruns, whose praise is thoroughly justified in my experience. I would be lost without it. Before and after eye operations, in all chronic and acute purulent affections of the conjunctiva, it is of great value. The solution, however, should always be fresh. After instilling the argyrol, I wait a few minutes and then irrigate the eye with tepid boric acid solution to remove the coagulated masses of mucus.

While protargol is of great germicidal value, I have supplanted its use by argyrol, owing to the irritating effects of the former.

Copper sulphate in the shape of the copper stick is indicated in trachoma.

Zinc sulphate or chlorid, valuable astringent in all inflammations of the conjunctiva, possesses specific bac-

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tericidal effects in cases of diplobacillary conjunctivitis.

Alum, in the shape of the stick, is a good astringent for applying to limited portions of the inflamed conjunctiva.

Among the vegetable astringents, tannic acid is valuable as an ingredient for collyria for home use as well as for application in the office.

MIOTICS

Of the different salts of physostigmin, I have found the salicylate most satisfactory. Physostigmin is a very efficient contractor of the pupils and a stimulator of the ciliary muscle. It is therefore very valuable in the medical treatment of glaucoma. However, it is a drug that should be used with precaution, and the solution should not be stronger than is necessary for obtaining the result desired. A strong solution for hastening the disappearance of medicinal mydriasis is often very uncomfortable and disturbing. In long continued use of even weak solutions it may after a while become a marked irritant, the conjunctiva showing a condition not unlike the conjunctivitis from atropin. In some cases its effect is less severe, the patient complaining merely of irritation after its use, and the eye exhibiting a hyperemia of the ocular conjunctiva with a mild circumcorneal injection. In cases of simple chronic glaucoma with only a moderate increase of tension, I have seen very disastrous results from one installation of a strong solution of physostigmin (1 per cent. solution). The following case will illustrate this point:

A woman had used for a long period a solution of physostigmin salicylate (1/10 grain to 1 ounce) in each eye twice a day with a very satisfactory effect on the intra-ocular tension. While the patient was in a distant city, the bottle containing the physostigmin solution was broken. Fearing to go without it, the patient requested a physician to give her a prescription for a solution of physostigmin. Within two hours after the instillation of a 1 per cent. solution, an acute attack of glaucoma supervened, which later required an operation.

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Pilocarpin hydrochlorid is milder and less irritating than physostigmin, and I prefer it in all cases to hasten the disappearance of mydriasis, and in the majority of cases of glaucoma. I have used it in solution as strong as 2 per cent., and, so far, have not found that any irritating or painful effect has resulted from its use. It is often happily combined with a small amount of physostigmin salicylate. In all collyria containing miotics, boric acid is also added.

SUBCONJUNCTIVAL INJECTIONS

The eye lends itself well to subconjunctival injections owing to the ease with which they can be employed, readiness of absorption, and facility for noting the effects. In properly selected cases, with the majority of drugs used the injection is painless.

Ophthalmic surgeons have used, subconjunctivally, a great variety of drugs in many types of ocular lesions. Darier especially has had great experience in ocular therapeutics of this nature. While I have used subconjunctival injections for a number of years, my list of drugs for that purpose is still small. The subconjunctival use of holocain and epinephrin has been mentioned under local anesthetics.

Among the other remedies with which I have had most experience are sodium salicylate, sodium iodate and citrate, guaiacol, mercuric cyanid and oxycyanid and sodium chlorid. In regard to the use of the solutions of the salts of mercury, I feel that they are of real value, but I also feel that they have at times been used rather unnecessarily and unwisely. For example: With a limited infected ulcer of the cornea, a thorough sterilization by drugs or cautery or by use of the thermophore, followed by a treatment every two hours with antiseptics and a bandage between treatments, the ulcer will heal without the use of mercuric cyanid. It is well to remember Darier's expressed contraindications to the use of subconjunctival injections "when

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there is present circulatory stasis, rendering absorption of medicaments difficult or impossible by the obstructed lymphatics. Under such circumstances, mercuric cyanid injected beneath the conjunctiva will act as an irritant more harmful than useful, and producing intense pain and chemosis." I have seen several such cases with infected corneal ulcer in which the mercuric cyanid injection had been followed by unpleasant results. Patients, too, complain bitterly of the pain following its use in uveal inflammations, detached retina, etc.

When the specific action of a drug is not called for, but when it is desirable to promote absorption of extravasated blood, inflammatory exudations, or the fluid under a detached retina, physiologic sodium chlorid solution acts admirably in the latter stages after acute conditions have passed away. It is painless, causes very little reaction, and it can be repeated as often as every other day. It is especially effective if associated with other remedies, including rest in bed.

CONCLUSION

In our justifiable enthusiasm over the great achievements of Pasteur and Lister, we have had rather too much tendency to consider the one great factor in infection to lie in the invading bacilli and their toxins, the while overlooking the equally great factor of bodily and tissue resistance. Fortunately, the serious study of food products of late is tending to the correction of this error. This research work is not only of large value in the various so-called nutritive disturbances of the eye, but of great assistance in cases of bacterial infections as well. "One man's meat is another man's poison" is well exemplified in the study of food sensitization in certain obscure ocular manifestations.

Preventive medicine is making vast strides. But in ocular affections we shall still have to rely, for many years, on the so-called curative measures—not the least of which are drugs.

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THE VALUE OF DRUGS IN UROLOGY*

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The entire genito-urinary tract may be reached for treatment by drugs, so that the pharmacologic armamentarium is large. Many of the therapeutic usages have come about empirically and have slender foundation of a scientific nature, and yet one hesitates to throw out drugs in which many of the older practitioners of wide experience place great confidence.

In order to arrive at a basis for constructing this article, a list of drugs applicable to urology was prepared from "Useful Drugs" and "New and Nonofficial Remedies" and sent out to some thirty of the best known urologists in this country. It was requested that they indicate which of the drugs mentioned were in their opinion actually useful. The list, with the number of affirmative votes each drug received, is given on the following page.

CRITICISM OF VOTE

It is interesting to note that only eighteen drugs receive the approval of 50 per cent. of the urologists, and only twenty-five, 30 per cent. It is safe to say that almost any one can get along without those after the first forty drugs (with the exception of a few new drugs like mercurochrome, benzyl benzoate and benzyl alcohol, which were not submitted to the vote). Hexamethylenamin stands first in the list, although it it safe to say that as usually given it is almost inert.

* From the Brady Urological Institute, Johns Hopkins Hospital.

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LIST OF DRUGS USEFUL IN UROLOGY

GIVEN IN ORDER OF POPULARITY AMONG TWENTY-SEVEN UROLOGISTS

1. Hexamethylenamin	27	36. Yellow mercuric oxid	6
2. Silver nitrate	26	37. Collargol	6
3. Potassium permanganate	25	38. Buchu	5
4. Argyrol	24	39. Arheol	5
5. Potassium iodid	23	40. Mercurialized serum	5
6. Neo-arsphenamin	22	41. Sajodin	5
7. Arsphenamin	21	42. Mercurial oil	4
8. Boric acid	21	43. Sodium arsenate	4
9. Oil of santal	21	44. Arsenous oxid	4
10. Protargol	20	45. Calomelol	3
11. Mercuric chlorid	20	46. Iodocasein	3
12. Sodium acid phosphate	20	47. Cresol	3
13. Tincture of iodin	17	48. Cubeb	3
14. Mercuric salicylate	17	49. Cargentos	3
15. Balsam of Peru	17	50. Neisser bacterin	3
16. Glycerin	17	51. Carbosant	2
17. Sulphate of zinc	16	52. Santyl	2
18. Phenol	16	53. Potassium mercuric iodid	2
19. Mercureal ointment	13	54. Silver citrate	2
20. Ammoniated mercury	12	55. Silver lactate	2
21. Acriflavine	12	56. Solargentum	1
22. Aluminum acetate	11	57. Sophol	1
23. Hydrogen peroxid	11	58. Protargentum	1
24. Sodium iodid	10	59. Gonococcus bacterin	1
25. Gonococcus vaccine	10	60. Scomin	1
26. Calomel	9	61. Dubois' iodolein	1
27. Mercuric iodid	8	62. Red mercuric oxid	1
28. Zinc chlorid	8	63. Electr-Hg	0
29. Hydrastis	8	64. Iodalbin	0
30. Mercurous oxycyanid	8	65. Lipoiodin	0
31. Methylene blue	7	66. Iodalbin and mercurol tablets	0
32. Alum	7	67. Mercuric benzoate	0
33. Copaiba	6	68. Mergal	0
34. Mercuric cyanid	6	69. Ammonium iodid	0
35. Mercuric succinamid	6	70. Arsenous iodid	0

The following are given as indicating preference in arsenicals:

71. Arsenobenzol	14	75. Neosalvarsan	9
72. Novarsenobenzol	10	76. Neodiarsenol	9
73. Salvarsan	11	77. Arsaminol	3
74. Diarsenol	10	78. Neoarsaminol	3

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Recent experiments by Burnham [1] and Hinman [2] have shown that, unless the urine is quite acid, formaldehyd is not liberated in the kidney in sufficient quantity to be germicidal or even inhibitory. Water should be drunk sparingly—the urine should not be too dilute—and acidifiers, such as acid sodium phosphate and sodium benzoate, 40 grains daily, should be taken along with large doses of hexamethylenamin (from 60 to 90 grains daily) to be of value. It is proper to insist on frequent tests for formaldehyd in the urine, as shown by Shohl.[3]

Silver nitrate is, of course, indispensable as being probably the most important antiseptic and caustic in chronic inflammations and ulcerations. But it is interesting to note that the next two in popularity, potassium permanganate and argyrol, have been shown experimentally to be very weak antiseptics. Their value undoubtedly is due to the fact that they produce little reaction and irritation. Potassium iodid, the arsphenamins and various mercurials are essentials, but it is interesting to note that mercuric salicylate has displaced the iodids of mercury, although the ancient mercurial inunctions still rank high. The gray oil used by the British and mercuric cyanid and the benzoate, so popular in France, are little used in America. This "plebiscite," however, is hardly fair or sufficiently thorough as to antisyphilitic drugs.

The rest of the list speaks for itself and is silent testimony to the fact that the urologist is not a polypharmacist, and that many widely heralded and much advertised preparations have not proved acceptable.

STUDY BY CLASSES OF DRUGS USED IN UROLOGY

Local Anesthetics.—So many fatalities and severe intoxications have followed the use of cocain (espe-

1. Burnam, C. F.: An Experimental Investigation of the Value of Hexamethylenamin and Allied Compounds, Arch. Int. Med. **10**: 324 (Oct.) 1912.
2. Hinman, Frank: Urinary Antisepsis, J. A. M. A. **65**: 1796 (Nov. 20) 1915.
3. Shohl, A. T., and Deming, C. L.: J. Urol. **4**: 419 (Oct.) 1920.

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cially when previous instrumentation, traumatism or ulceration was present) that it has been abandoned by careful operators. Alypin proved to be safer than cocain, as did eucain; but procain (novocain) which is one-tenth as toxic as cocain, has been shown to be so much safer than either of these that it is now almost universally adopted, a 2 to 4 per cent. solution sufficing for the urethra, prostate and bladder for ordinary instrumentation, urethroscopy and cystoscopy—sometimes supplemented by morphin hypodermically in nervous patients or for very painful procedures. For urologic operations a 1:400 solution of procain infiltration is effective not only for minor operations, but for prostatectomies, vesiculectomy for tuberculosis, etc.

Saligenin has been recommended recently as a urethral anesthetic "only one fifth as toxic as procain" by Hirschfelder and associates.[4] Macht[5] has highly recommended benzyl alcohol as a local anesthetic of efficiency, nontoxic (only one-fortieth that of cocain) and antiseptic in 2 per cent solution. It has been tried in my clinic with success, but in some cases proved irritating. Investigations by Macht and Shohl[6] showed that this was due to the formation of small amounts of benzoic acid when in alkaline glass containers, and that it can be eliminated by use of "nonsoluble glass." It has also proved very satisfactory for infiltration anesthesia. Macht and Satani[7] found that apothesin, eucain and holocain have also a slight antiseptic action, but not so great as benzyl alcohol, while cocain and procain were found by them to be entirely devoid of antiseptic properties. Apothesin has been shown by Eggleston and Hatcher[8] to be much more toxic than procain,

4. Hirschfelder, A. D., and Wynee, H. M. N.: Saligenin as a Local Anesthetic for the Female Urethra, J. A. M. A. **75**: 1770 (Dec. 25) 1920. Hirschfelder, A. D., Lundholm, A., and Norgard, H.: J. Pharmacol. & Exper. Therap. **15**: 261 (June) 1920.
5. Macht, D. I.: J. Pharmacol. & Exper. Therap. **11**: 419 (July) 1918.
6. Macht, D. I., and Shohl, A. T.: J. Pharmacol. & Exper. Therap. **16**: 61 (Aug.) 1920.
7. Macht, D. I., and Satani, Y.: J. Urol. **4**: 347 (Aug.) 1920.
8. Eggleston, C., and Hatcher, R. A.: J. Pharmacol. & Exper. Therap. **13**: 433 (Aug.) 1919.

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which however, is a vascodilator and should therefore be used in conjunction with epinephrin. Wesson has shown that by injecting a 10 per cent. solution of benzyl alcohol in olive oil into perineal prostatectomy wounds through the drainage tube and into the depths of the wound, the gauze packs may be more easily and almost painlessly removed.

Internal Urinary Antiseptics.—For many generations a great list of drugs have been recommended as urinary antiseptics, etc. We have not space even to name a small portion of them: santal, copaiba, cubebs, juniper, buchu, hexamethylenamin and methylene blue are among the best known. Of the first three, oleum santali is recognized perhaps to be the best. While modern scientific investigation has tended to discredit its value, our urologic plebiscite shows it still to be in popular favor—particularly in acute gonorrhea.

Hexamethylenamin is chiefly excited in the urine and gives rise to formaldehyd in the presence of free acid. When urine is alkaline this decomposition does not occur and the drug is not effective. The drug should be given in good quantity (from 60 to 90 grains daily), water restricted and acid sodium phosphate (administered between doses of hexamethylenamin) from 5 to 10 grains every four hours to insure marked acidity of urine. Its main usage is to prevent instrumental infection of the bladder.

Investigations have been carried out at the Brady Urological Institute by Davis and White[9] with the object first of producing a compound with phenolsulphonephthalein which would be eliminated in the urine as an antiseptic, and one such compound, chlormercury fluorescein, experimentally possessed all the required properties—produced antiseptic urine without injury to the animal.

9. Davis, E. G., and White, E. C.: J. Urol. 2: 107 (April) 1918; 2: 257 (Aug.) 1918.

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CLINICAL USE OF VARIOUS DRUGS IN UROLOGY

DIAGNOSIS

(*a*) Urine: analysis: usual reagents, stains, culture mediums (especially for gonococcus).

(*b*) Urethral, seminal vesicle and prostatic secretion: acetic acid, stains, etc.

(*c*) Kidneys: analysis of separated urines, as given (*a*). Function tests; phenolsulphonephthalein (best); indigocarmin (rarely).

(*d*) Roentgen ray: pyelograms, cystograms; thorium nitrate (15 per cent.), sodium bromide (15 per cent.).

(*e*) Blood chemistry: reagents for blood urea, creatinin.

GENERAL

(*a*) Local anesthetics: procain (1 to 4 per cent. urethral injection); benzyl alcohol (1 to 4 per cent.).

(*b*) External antiseptics: soap and hot water; mercuric chlorid, alcohol; tincture of iodin; potassium mercuric iodid (Kalmerid).

(*c*) Lubricants: liquid petrolatum; glycerin; tragacanth paste (KY); petrolatum; olive oil.

(*d*) Coagulants, styptics: epinephrin; silver nitrate; copper sulphate; horse serum; blood transfusion; cephalin.

EXTERNAL INFECTIONS (BALANITIS, ULCERS, CHANCROIDS, BUBOES, CHANCRES)

1. Washes: boracic acid; potassium permanganate, silver nitrate, mercuric chlorid mercurochrome, copper sulphate, phenol.
2. Dusting powders: lycopodium, boric acid, iodoform (rarely), calomel.
3. Ointments: boric acid; mercurochrome; zinc oxid; ammoniated mercury; balsam of Peru; scarlet R.
4. Caustics: silver nitrate; phenol; nitric acid; copper sulphates; cautery; fulguration.
5. Wet dressings: saline (chancres until discovery of spirochetes—later arsphenamin powder?).

INFECTIONS OF GENITO-URINARY TRACT

1. Urethritis: (*a*) Acute (anterior and posterior, prostatitis, vesiculitis, epididymitis)
   1. Diluents: internal antiseptics; water forced, sodium bicarbonate; potassium citrate and hyoscyamus; santal oil; hexamethylenamin(?).
   2. Injections: argyrol; protargol; acriflavine; mercurochrome; silver nitrate (later); zinc sulphate.
   3. Irrigations: potassium permanganate; mercuric chlorid; silver nitrate; acriflavine; mercurochrome; mercuric oxycyanid.
   4. Antispasmodics: hyoscyamus; belladonna; extract of opium (supositories); morphin, papaverin.
   5. Heat: stupes; hot water bag to perineum; hot rectal douches; hot sitz baths, etc.
   6. Cold: ice applied to external genital or perineum, or by two-way rectal douche.

   (*b*) Chronic
   1. Same drugs as above, according to circumstances.
   2. Instrumentation: urethroscopic applications (silver nitrate, stick or in solution); instillations of silver nitrate 1 to 5 per cent.
   3. Mercurochrome, 1 per cent., after massage of vesicle and prostate and cleansing irrigation.

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2. Prostatitis, vesiculitis (*a*) Acute: as above, 1 *a*, as circumstances may require, with rest in bed and frequent cold rectal irrigations.
   (*b*) Chronic: as above, 1 *b*: also injections of vas deferens and vesicles through vasotomy or urethroscope with protargol, argyrol, collargol or mercurochrome.
   (*c*) Tuberculous: injection (after epididymectomy) through vas; phenol (pure); iodoform oil.

3. Cystitis:
   (*a*) Acute: 1. Internally; forced water; potassium citrate; hyoscyamus (if painful); if not painful, reduced water, sodium benzoate and hexamethylenamin. 2. Irrigations: salt solution; boric acid; potassium permanganate; mercuric chlorid; silver nitrate; mercurochrome; acriflavine. 3. Injections and instillations: silver nitrate; mercuric chlorid; argyrol; protargol; mercurochrome.
   (*b*) Subacute: Same as above, more vigorously, to sterilize bladder; yeast; Bulgara tablets.
   (*c*) Chronic: Same as above, more vigorously, to sterilize bladder; yeast; Bulgara tablets.
   (*d*) Ulcerative and interstitial: cystoscopic applications; silver nitrate; phenol; cautery; fulguration; excision.
   (*e*) Tuberculous: Gomenol; phenol (10 per cent. injection); iodin (gas); mercurochrome (1 per cent. injection); fulguration.

4. Pyelitis:
   (*a*) Acute, febrile: forced water (internal); sodium bicarbonate (sometimes alkalis forced, especially in children).
   (*b*) Acute, afebrile: (1) Water reduced (internal); acids forced (sodium benzoate; sodium acid phosphate); hexamethylenamin (60 to 90 grams each day). (2) Pelvic lavage: silver nitrate (1 to 5 per cent.); mercurochrome (1 to 5 per cent.). (3) Pyelogram: thorium nitrate (15 per cent.); sodium bromid (15 per cent., to determine advisability of operation).
   (*c*) Pyelonephritis: Same as *b* 1 and 2 as circumstances may require; nephrectomy of unilateral.
   (*d*) Ureteritis: Same as *b* 1 and 2 as circumstances may require; with dilatation of strictures, if present, using bougies and paraffin bulbs.

5. Kidney, hematuria:
   1. Internal: ergot, etc.; horse serum; blood transfusion; calcium chlorid; gelatin.
   2. Pelvis lavage: silver nitrate (1 to 5 per cent.); epinephrin (1 to 5 per cent.).
   3. Pyelogram: thorium nitrate (15 per cent.); sodium bromid (15 per cent.) to exclude neoplasm, stone or tuberculosis.

6. Kidney, impairment (back pressure from prostate, etc.):
   1. Relief of obstruction: catheter or suprapubic drainage; irrigations to prevent infection.
   2. Internal diuretics: forced water (6 to 12 quarts daily); saline infusions; transfusions; rectal drip.
   3. Cardiac stimulants: digitalis (infusions).
   4. Cardiorenal diet.
   5. Function test: phenolsulphonephthalein; blood urea; creatinin.

7. Kidney, suppression (anuria):
   1. Water and diuretics as above.
   2. Bloodletting and simultaneous opposite intravenous saline.
   3. Application of heat; baths, stupes, hot water bottles, etc.; sweat baths.
   4. Pelvis lavage: sterile salt solution or mild antiseptic.

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Further experiments showed that both acriflavine and proflavine given intravenously in rabbits (5 mg. per kilogram) produce antiseptic urine without injury to the animal. The rabbit's urine is alkaline. The same drugs failed in dogs whose urine is acid. Davis [10] has recently carried out similar studies with 204 anilin dyes, fifteen of which were efficient as antiseptics when added to voided urine, were excreted by the kidney and were nontoxic. Only two of these, acriflavine and proflavine, produced antiseptic urine (as previously shown). Clinical tests have not yet been made. There is great hope of accomplishing valuable results along these lines in the near future. Davis thinks that dyes of the triphenylmethane, xanthone, acridin and azin groups (particularly the latter) give more promise of success.

Local Germicides and Antiseptics in Urology.—Since most inflammatory diseases of the urinary tract consist, at least in their early stages, of a superficial inflammation of the lining muccus membrane, it was early thought that they could well be treated by the local application of germicidal substances, which would destroy the causative organisms. Almost every germicide and antiseptic has been utilized in this manner.

In considering a given substance, its suitability must be determined according to (1) whether it forms a precipitate with albuminous material; (2) whether its germicidal or antiseptic power is diminished by the presence of albuminous material; (3) the strength at which it can be used without irritation, and (4) its ability to penetrate the tissues while retaining its germicidal or antiseptic effect. As urinary infections progress, they become more and more deep-seated, so that sooner or later they pass beyond the sphere of effect of drugs applied locally. For this reason it is difficult to estimate the extent of the germicidal or antiseptic action of a drug in a given case. It is still

10. Davis, E. G.: Am. J. M. Sc. **161**: 251-257, 1921.

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by no means clear how much of the favorable action of these drugs is due to their germicidal or antiseptic action, and how much to cleansing effects or local stimulation of tissue reactions. In addition, it seems probable, since in many cases the treatment is effectual while the infecting organism can still be found in the secretions, that antiseptic action is often an important element where complete destruction of the bacteria cannot be accomplished.

One of the first drugs recommended for its germicidal action in the urinary tract was mercuric chlorid. Owing to its irritant nature, it must be used in high dilutions, such as from 1:20,000 to 1:60,000. It precipitates albuminous matter, thus forming a more or less impermeable barrier to its own action, and losing at the same time a great part of its germicidal power. It has fallen almost entirely into disuse, and it seems probable that its good effects were almost entirely due to the cleansing effect of the large quantities which were used.

This principle of irrigation with a large quantity of solution was especially emphasized by Janet, who introduced potassium permanganate for the purpose. This drug is reduced by contact with protein material, giving up "nascent" oxygen. Its germicidal action is therefore transitory. It is usually employed in weak solutions, such as from 1 to 2,000 to 1:10,000, and it is not likely that such solutions are effective germicides, since it has been shown that a 1:4,000 solution fails to kill the gonococcus in twenty minutes. As a mildly stimulating and cleansing remedy it has value, however, and has won the most widespread use.

Lead acetate, zinc sulphate, aluminum acetate and copper sulphate have been extensively used, especially in gonorrhea, but their germicidal activities in suitable concentrations are nil, and they have their effects entirely by virtue of cleansing astringent or stimulating actions. Phenol also is inactive in the strengths recom-

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mended, failing to kill the gonococcus in a 1 : 400 dilution in twenty minutes. It has had some vogue as a prophylactic. Guaiacol has been used locally in cystitis. Its germicidal powers are comparable to those of phenol. Boric acid is practically devoid of germicidal action, and while it may have a certain antiseptic property, its solutions are useful only for their cleansing effects. It is now seldom used.

Silver nitrate has been used very extensively. It is a powerful germicide, but suffers from the same disadvantages as mercuric chlorid. As injection and irrigation in the urethra in acute cases it has been almost entirely replaced, and is used principally for topical application or instillation, or in the bladder or renal pelvis, where its irritant and stimulant properties account for a large part of its effectiveness.

Efforts to produce a silver preparation free from the irritating properties of silver nitrate led to the introduction of collargol and the silver albuminatès, many of which have been recommended under the names protargol, argyrol, silvol, cargentos, etc. While these drugs are nonirritating and are not protein coagulants, they have very weak germicidal powers. It is also probable that, owing to the fact that they are colloidal suspensions instead of true solutions, their penetrating qualities are slight. They may be used, however, in concentrated form, and they are certainly beneficial in many cases of gonorrheal urethritis. They are not by any means the best in cystitis or pyelitis, and while undoubtedly superior to silver nitrate in acute gonorrhea, do not represent the ideal of a local urinary germicide. Similar compounds of mercury and albumin have been produced and recommended, but apparently have no advantages.

The fact that certain dyes exercise powerful and often strongly selective effects on bacteria led Browning to try them in urinary infections. He found in brilliant green a useful treatment for gonorrhea, but

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later proflavine and acriflavine proved to be even better. Of these, acriflavine has had the most success. This dye is rather irritating to the urinary mucosa in strengths greater than 1:1,000. However, it does not coagulate protein, and it is stated that its germicidal action is not diminished in the presence of serum. This property distinguishes it from practically all of the other known germicides. The flavines apparently produce their germicidal effect by a mechanism entirely different from that of the metallic germicides. This is indicated by the behavior toward serum mentioned above, by the fact that very small factors, such as change in reaction or in the salt content of the test solutions, will alter greatly the germicidal activity, and by the results of experiments reported by Gray and Morrison.[11] They found that concentrations of acriflavine many times greater than necessary to kill a certain organism in the test tube were entirely without effect on the course of an experimental empyema produced by the same organism. The effect of acriflavine develops slowly, requiring a long exposure for the best results to be produced. Under favorable conditions acriflavine [10] shows very high germicidal powers, and many observers believe it to be a most successful drug in the treatment of gonorrhea. In Germany, extraordinarily high germicidal powers are claimed for it. It is used as an injection at a strength of 1:1,000, or an irrigation at a strength of 1:5,000.

Recently Young, White and Swartz [12] have described a compound of fluorescein and mercury designed to have both the penetrative power of the dye and the germicidal activity of the mercury. This drug is known as mercurochrome. It does not coagulate albumin although, like all mercurials, its activity is some-

11. Gray, F. P., and Morrison, L. F.: J. Infect. Dis. **28**:1 (Jan.) 1921.

12. Young, H. H.; White, E. C., and Swartz, E. O.: A New Germicide for Use in the Genito-Urinary Tract: "Mercurochrome 220," J. A. M. A. **73**:1483 (Nov. 15) 1919.

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what reduced in the presence of serum. It is comparatively nonirritating, being borne in the urinary tract in strengths of 1 per cent. or even more, and is a powerful germicide. It is effective in a short time against all the ordinary organisms, and kills the gonococcus in twenty minutes at a strength of 1:16,000. In urine, 1:800 kills the colon bacillus in one minute. It has an intense red color. It has been used in pyelitis, cystitis, gonorrhea and other conditions with many very excellent results. The rapidity with which a 1 per cent solution will often sterilize a foul, badly infected bladder is remarkable. In gonorrhea, it is equally effective as argyrol and as acriflavine, which is probably the antiseptic of choice on account of its lack of staining quality.

Other drugs which have not been widely used have some interest in connection with urology. Chlorazene has been recommended for employment on the urinary tract. It kills the gonococcus in twenty minutes at a strength of 1:3,200. It has proved to be irritating, however, and has found little use. The tricresols, though much more effective germicidally than phenol, are still very weak, and would seem to have no place except possibly to replace phenol in prophylactic combinations. Potassium mercuric iodid is equal if not superior to mercuric chlorid as a germicide, and does not precipitate albumin at all. While rather irritating, it seems that it might be useful when an irrigation fluid having more lasting germicidal properties than those of potassium permanganate is desired. The effectiveness of soap in venereal prophylaxis has long been known, and it has recently been shown that sodium oleate, especially if combined with a little boric acid when albuminous matter is present, is quite an active germicide for the gonococcus, killing it in twenty minutes at a dilution of 1:3,000. Very weak solutions are effective in increasing considerably the germicidal power of other drugs against the gonococcus. It is tolerated by the

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urinary mucosa in strengths of 1:200. While entirely inert against *Bacillus coli* and the staphylocci, it would seem advantageous to make use of this gonococcicidal power of soap, in conjunction with its cleansing properties, in the urinary tract.

In the urethra, various methods of applying germicidal substances have been recommended. Some urologists, after introducing such drugs as argyrol or acriflavine in early cases of gonorrhea, have sealed the meatus shut, keeping the drug in contact with the seat of infection for many hours. Others have sought to attain the same end by mixing the drugs with viscid or greasy menstrums, such as one of the gums, lanolin, or aluminum hydroxid, which will remain in the urethra for some time. It would seem that if the most effective germicidal action is to be secured, the drug should remain in contact with the seat of infection for the longest possible time.

While many powerful germicides have been used in the urinary tract, no uniform success has attended any of them. It seems probable that this is due largely to the depths to which the inflammation extends in most cases. There is little doubt, however, that as our selection of suitable drugs increases, more and more cases are responding to germicidal applications. There is unquestionably a great future for germicidal treatment in venereal prophylaxis, in acute gonorrhea, and in other infections of the urinary tract.

An extended clinical study of various mercurial preparations which have been prepared by White in the chemical laboratory of the Brady Urological Institute is being conducted with the aid of funds from the Interdepartmental Social Hygiene Board. The first of these studies to be published is on mercurochrome, already referred to, which has been shown, by numerous clinical investigators, to have a wide range of usefulness not only in urology, but also in gynecology, otolaryngology, ophthalmology and general surgery. It

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has proved a remarkable drug in the treatment of diphtheria carriers, Gray and Mayer reporting complete success in eighty-eight out of ninety such cases.

The chief objection to mercurochrome is its deeply staining quality which, probably contributing greatly to its germicidal action, makes it objectionable to patients, especially as an injection for gonorrhea. We have consequently been searching for a penetrating, highly germicidal drug which does not stain, and in two new mercury preparations, known at present merely as 245 and 253, we have powerful germicides, nontoxic, nonirritating and nonstaining, which are being tested out clinically with apparent success. But much has been accomplished already; and with silver nitrate, argyrol, protargol, acriflavine and mercurochrome, great success is now obtained in curing chronic infections of the renal pelvis, bladder, prostate, vesicles and urethra, which only a few years ago were considered beyond therapeutic assistance.

Sedatives and Antispasmodics.—The opiates morphin, codein by mouth or hypodermically and extract of opium by suppository have been widely used in urology, often in conjunction with belladonna or hyoscyamus. Recently other alkaloids of opium have been advocated, and Macht [13] has made a study, here, to determine their respectiye value not only in relief of pain but also in spasmodic conditions of the ureter, bladder and urethra. It has been shown that while morphin and codein relieve ureteral and vesical colic through their action on the pain centers of the brain, their effect on the contraction and tonicity of the ureters and bladder is stimulating. Papaverin, however, while not being a powerful central analgesic, exerts a remarkable relaxing or antispasmodic effect on smooth muscle. On this account it has been used at this clinic to facilitate the passage of a ureteral

13. Macht, D. I.: J. Pharmacol. & Exper. **11**: 389 (June) 1918.

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calculus, a solution of papaverin being introduced by ureteral catheter.[14]

A combination of the different opium alkaloids, such as pantopon, contains a sufficient amount of papaverin alkaloids to counteract the stimulating peripheral effects of morphin on smooth muscle. For this reason pantopon has proved more efficient than morphin clinically in relieving colicy pains in general, and ureteral and vesical pains in particular.[15]

Likewise benzyl benzoate [16] has proved efficient in these conditions. In subacute renal and vesical pains this drug may be given by mouth, from 2 to 4 c.c. of the 20 per cent. alcoholic solution, three or four times a day.

Recent experiments at this clinic show that the action of the different belladonna alkaloids (atropin, hyoscyamus, scopolamin) as antispasmodics for the bladder is not the same, and for this reason the galenical preparations of hyoscyamus are probably more sedative than those of belladonna. The ancient treatment which contains potassium citrate and tincture of hyoscyamus, each 2 drams, to water, 6 ounces; the dose 2 drams four times a day is of unquestioned value just as is the suppository containing each one-half grain of extract of opium and extract of hyoscyamus. Acetylsalicylic acid is of distinct value as an anodyne and sedative.

Heat applied to the perineum or by rectal irrigation or by sitz bath is important to relieve pain and spasm of bladder, prostrate and urethra.

Diuretics.—Those which have had the widest usage are: water (forced), digitalis (infusion), caffein, theobromin sodium salicylate, potassium acetate, potassium citrate and heat. Of these the simplest and best is water given in large quantities by mouth (often from 10 to 12 quarts daily are taken in our clinic), and if

14. Macht, D. I., and Geraghty, J. T.: Bull. Johns Hopkins Hosp. 27: 119, 1916
15. Macht, D. I.: J. Urol. 1: 201 (April) 1917.
16. Macht, D. I.: J. Pharmacol. & Exper. Therap. 11: 419-446 (July) 1918.

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necessary this is supplemented by saline infusions (beneath the breasts) or by salt solution by rectum. In severe cases intravenous saline infusion is practiced, occasionally with simultaneous bloodletting from a vein of the opposite arm (in severe uremia or sepsis). This forcible hydrotherapy often accomplishes wonders, and speedily. It is contraindicated in general edema, anasarca, cardiac distress, etc.

Of the drugs named above, caffein modifies the circulation by stimulating the heart and relaxing the vessels by direct action. The flow of urine is thus increased. It is most efficient in cardiac dropsy. Digitalis has a similar action, stimulating and greatly improving the heart output, which relieves congestion and dropsy and increases the flow of urine. Theobromin sodium salicylate has an action on the heart and kidney similar to caffein, but has less effect on the central nervous system and is therefore better as a diuretic. It is non-irritating to the kidney (dose from 5 to 15 grains three times a day).

Of the saline diuretics, potassium acetate and potassium citrate are the most useful. Potassium acetate is used as a diuretic in nephritis and to render the urine alkaline and less irritating. It is an effective diuretic, increasing the solids in urine without irritating the kidneys. The dose is 15 grains every three hours (for a limited time). Potassium citrate acts like the acetate, but is less readily absorbed and is more laxative. Magnesium sulphate is not only an active saline cathartic, but a valuable diuretic from the small portion absorbed. This should often be the purgative chosen in cases of uremia. Heat is most valuable and may be applied as hot stupes over the kidneys to stimulate action, or as sweat baths, tubs, etc.

Aphrodisiacs.—This subject is still obscured with the mists of antiquity which have enveloped the search for the fountain of youth. Cantharides has always occu-

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pied a hallowed place, but its usage has never been scientifically directed, although recent experiments in the pharmacologic laboratory here indicate that it is still one of the most valuable aphrodisiacs so far known. Yohimbin has been highly commended, but experiments do not seem to confirm the claims made. Strychnin is of value, but phosphorus, damiana, saw palmetto, etc., have been found to be of little use. Further study is required and is in progress in this clinic.

As a rule, sexual impairment (either in desire, erections or ejaculation) is due to an inflammatory condition of the verumontanum, prostate and vesicles, and is best treated by massage, and applications of silver nitrate to the verumontanum through the urethroscope, etc., instillations of mercurochrome, etc.

Anaphrodisiacs.—These are mainly necessary to prevent priapism following operations on the penis, or chordee in acute gonorrhea. Potassium bromide in large doses (from 20 to 30 grains) repeated frequently are often required, and may not be successful. In other cases scopolamin has been found useful, and some have recommended the use of vanillin. Ice packs may also be very helpful.

Antisyphilitics.—For many years syphilis has been one of the few diseases in which it was known positively that drugs were of definite value. With mercury and potassium iodid remarkable results were obtained, but many sad examples of blasted hopes of permanent cure constantly occurred, and after the demonstration of *Spirochaeta pallida* as the causitive agent, it was shown that chronic diseases of the central nervous system and spinal chord were nearly always due to syphilis.

Hope was restored when Ehrlich brought out arsphenamin, and in the wild claims of quick sterilization by a few intravenous injections, each of which amounted to a surgical operation (with "appropriate" prices),

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all discretion and the experience of years (based on the sure foundation of generations of experience with mercury and potassium iodid) were cast to the winds —resulting in great harm to the medical profession from which it has not yet recovered.

At last a realization is dawning that the arsenicals alone rarely cure, and that great reliance has to be placed in mercury and potassium iodid. Although investigations by the score are going on, there is little that is certain about the drugs or definite as to clinical usages. During the war, the Allies and Germany were agreed on one thing—the treatment of syphilis. All used neo-arsphenamin and mercury simultaneously or intermittently. With the American army, we so simplified the technic that only 2 c.c. of sterile distilled water was used and the solution was made in the neo-arsphenamin ampule itself, and injected with an ordinary hypodermic needle, in the field hospitals at the front.[17] In civil life such simplification is not necessary, and recent laboratory experiments with syphilitic rabbits show that arsphenamin is definitely more positive in results, and most anthorities think it should be preferred. Mercurial oil and calomel, so popular in Europe, have recently been shown to be far inferior in absorption to the salicylate. For quick effect the cyanid used intravenously, is to be preferred. Inunctions remain very popular, despite drawbacks. The benzoate is little used in America. The Wassermann test has been somewhat discredited and the luetin test completely so. There is no agreement among "authorities" and "experts," and spinal punctures show an increasingly greater number of infections. The need of continuous treatment for many months is again being strongly urged.

Improvements in drugs, both arsenicals and mercurials, are badly needed. Many experiments are being

17. Young, H. H.: Preventive Medicine as Applied to Venereal and Skin Diseases, J. A. M. A. 73: 1668 (Nov. 29) 1919. Young, H. H., et al.: Manual of Military Urology, Paris, 1918.

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conducted, and we may hope for important announcements in the near future.

Organotherapy.—The pituitary gland has furnished useful drugs for the urologist. The posterior lobe substance, when given hypodermically, increases peristalsis by direct action on the musculosa of the intestine. We have found it of great value in abdominal distention which so often follows suprapubic or kidney operations and which may be so fatal. The drug may be used repeatedly and is almost always followed by a large escape of gas through the rectal tube, which should be employed simultaneously. (Physostigmin, given before and after operation, has not proved very helpful in our cases).

The anterior lobe of the pituitary has been shown to have a close relationship to genital development. In Goetsch's experiments with young white rats, fed on the anterior lobe, the testicles rapidly became much larger than in control animals of the same age. We have therefore employed it after operation in cases of undescended testicle and in other cases of poor genital development and sexual impairment. No adequate study of results obtained has been made.

The testis has been the subject of much experimentation, and successful transplantations followed by extraordinary sexual changes (even crossed sexes) have been reported. The testicular substance has also been used as a drug, as has also the prostatic substance. The therapeutic uses and limitations of these substances have not been sufficiently studied, and offer an excellent field for research.

Diagnostic Agents.—Certain drugs, while not of therapeutic value, are of the utmost importance in urologic practice as diagnostic agents and therefore must be named among the useful drugs. We need only mention the invaluable information given as to the kidney function by phenolsulphonephthalein and the diagnostic

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value of sodium bromid and thorium solutions in connection with pyelography. Radium has a wide field of usefulness in urology, as it may be applied through so many portals: the urethra, bladder and rectum, by perineal puncture (needling), and by suprapubic incision with insertion of tubes of emanations. The various drugs of clinical and bacteriologic laboratory usage are very needful in urology, which, with blood chemistry, renal function tests, the cystoscope and roentgen ray, has become one of the most exact of medical sciences.

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THE USE OF DRUGS IN NEUROLOGY AND PSYCHIATRY

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Nervous and mental disorders cover an extremely wide territory, much of which has hardly been explored. The types of disorders are numerous. The principles underlying the disorders are often obscure. In some disorders, as in the infections, the degenerations and the neoplasms, the same principles apply in neurology and psychiatry as in the field of internal medicine. In this group, we are dealing with symptoms of the reactions of the nervous system to infective agents, to poisons elaborated within the system or introduced from without, to changes in the vascular system, to neoplasms, to trauma, and to the degenerative changes of advanced life. In treating these disorders, the physician is dealing with familiar problems. He aims to destroy the infective agent, to eliminate or counteract the poisons, to supply deficient chemical substances, to regulate and safeguard the cardiovascular system, to check or remove the neoplasm, and to deal with the traumatic residual. In this work, he makes use of drugs according to the general principles outlined by Barker, counteracting the organismal irritants, regulating the disordered functions, and supporting the compensatory measures initiated by the various systems.

USE OF DRUGS IN VARIOUS DISORDER GROUPS

In another group of disorders, one has to keep in mind principles which are provisionally discarded by the internist and the other specialists. These dis-

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orders are not due to the disordered functions of a single system. They are the result of a conflict between different instinctive forces. They may be a method of adaptation, although an inferior one, to the difficulties of a complex social environment. Where such is the meaning of a disorder, it is obvious that the use of drugs must play a very subsidiary rôle, and the fact that these principles have been so frequently neglected makes the chapter of the abuse of drugs in neurology and psychiatry a somewhat lengthy one. Where a nervous or mental disorder is the expression of a definite structural or toxic involvement of the nervous system, the principles which determine the use of drugs require no special comment. Among the disorders of this group, the syphilitic disorders take the first place, and with regard to them the rôle of drugs has been most important. The introduction of arsphenamin has been the same boon to neurologic and psychiatric practice that it has been to the syphilologist. It is doubtful whether full advantage is taken of the possibilities of the drug. There is still a tendency to look on certain organic nervous diseases of syphilitic origin as not being amenable to this treatment. While this is partly true, the distinction has been taken in too absolute a sense, and it is not possible to foresee with absolute certainty whether a given case will benefit by the drug and if so, to what extent. Those who maintain that it is useless to treat a case of general paralysis of the insane fail to do justice to the actual results of intensive treatment carried on over a sufficiently long period, with the necessary variations in the method, intravenous, intraspinal, intradural, intraventricular or intracisternal. In differentiating the various forms of syphilitic involvement of the brain, the degree of resistance to treatment by arsphenamin is perhaps the most important point to emphasize, and this does not always go parallel with the prominence of those symptoms which

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we have been accustomed to associate with the fatally progressive type of disorder.

In regard to the treatment of tabes dorsalis, the experience of the various workers differs, but it can hardly be doubted that in some types of cases the symptoms are modified by the treatment.

SYMPTOMS REQUIRING SEDATIVE TREATMENT

In the other groups of organic nervous disorder, in which it is not a question of surgical procedure, treatment is more of a symptomatic nature. In the large group of disorders with involuntary movements (Parkinson's disease, choreiform and athetoid conditions, and various lenticular syndromes) a great variety of drugs have been employed for their sedative action; but, while they may reduce rigidity and stop the involuntary movements, the drugs employed are such that they cannot be continued indefinitely, and treatment for a limited period leaves no permanent improvement. In regard to Sydenham's chorea, the claims for benefit by treatment of the underlying infection by salicylates are not firmly established, and the traditional treatment with liquor potassii arsenitis (Fowler's solution) is more an indication of medical conservatism than of the virtue or arsenic. The motor restlessness in chorea may be so exaggerated as to make sedatives advisable, and it is not uncommon to see children treated with enormous doses of a great variety of sedatives. In many cases a child who is making little progress under such intensive drug therapy will derive the greatest benefit from having the drugs discontinued, and from being treated in a continuous warm bath. The results from subcutaneous injections of magnesium sulphate in chorea may turn out to be of therapeutic importance; the benefit from injections of sodium cacodylate in conditions of spasticity is only transitory, and of academic rather than practical interest.

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Of the disorders with motor symptoms, epilepsy is one in which drug treatment has been used for many years with little modification. This treatment consists of the bromids in various mixtures, combined with dietetic and general hygienic treatment. The treatment has been recognized to be merely symptomatic, and its drawbacks have been obvious. The introduction of luminal has, therefore, been welcomed in the treatment of epilepsy, all the more so as it is frequently beneficial in cases of quite severe type. It is, perhaps, premature to say whether, over a long series of years, the treatment will continue to give as good results as it at present promises to do. In hysteria, other types of convulsive episodes are encountered, and the drugs which are frequently used in this disorder belong to the chapter on the abuse of drugs in neurology and psychiatry. They are the pharmacologic evidence of the medieval trend which is still alive below the surface of the modern physician.

SYMPTOMS REQUIRING ATTENTION OF NEUROLOGIST

Of the various symptoms which demand attention from the neurologist and the psychiatrist, the most common are pain and distress, sleeplessness, agitation and excitement. These are the symptoms for which the physician has recourse to drugs, while the complex underlying disorders are recognized to be beyond the reach of such simple methods of treatment. It is true that claims have been made for the beneficial effects of certain tissue extracts in cases of pathologic lying; should it be possible to isolate the active principles and produce them synthetically, their application to the more familiar forms and the minor degrees of moral aberration would open a new chapter in the history of ethics.

As for the treatment of pain and distress and sleeplessness, the danger of a purely symptomatic treatment is well known. They are merely indicators of

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the underlying disturbance, and it is the business of the physician not to confine himself to the warning sign, but to penetrate to the underlying disorder. Merely to remove the disconcerting symptoms involves the double danger of neglecting the fundamental trouble, and of developing an ignoble dependence on the drug. But symptoms deserve some attention on their own account, and pain is the one which is the most insistent. The value of opium and its derivaties is familiar, and the pharmacologist is trying to find out that combination of alkaloids which gives the beneficial effects with the most certainty, and with the least disturbance of other functions. Some have warmly advocated the use of opium in the treatment of conditions of depression, recommending gradually increasing doses, with, later, gradual reduction. Although in an occasional case this treatment is followed by improvement, it is not to be depended on. Similar claims have been made for the beneficial treatment of cases of agitated depression with bromid pushed to the point of intoxication, but these claims, too, are still to be substantiated. For conditions of mental distress with agitation, barbital in comparatively small doses is a very useful drug.

Sleeplessness, too, is an indication that all is not well with the economy, and that it is time to make a detailed review of the personal balance. At the same time, it is frequently advisable to give some temporary help with regard to sleep. Paraldehyd is the drug which gives the nearest approach to a normal sleep, but, owing to its disagreeable odor, the coal-tar derivatives have been much preferred, and of the series barbital is the most uniformly satisfactory. A great number of new hypnotics are being continually brought forth, but the value of each requires some time to be established. Apart from sleeplessness, pain and mental agitation, the patients of the psychiartrist are apt to have conditions with considerable motor excitement,

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and here drugs in the past have been used to a deplorable extent, and in a routine and unintelligent way. Where now a patient is treated in a continuous bath without the use of any drugs, either for sedative or hypnotic purposes, the patients of a previous generation received their nightly dose of scopolamin. It is true that occasionally one has to resort to a sedative of this description in a wild, unreasoning excitement, but as a rule a case with considerable motor overactivity can be treated without scopolamin, or its equivalent, with a good nursing personnel, facilities for a continuous warm bath, and an occasional dose of paraldehyd.

If in psychiatry the use of drugs is somewhat limited, it is largely because in these complex disorders the chief weight in the treatment must be laid on the personal relationship between physician and patient, on the organization of the nursing personnel, and on the atmosphere of the hospital with its occupational and recreational elements. It is in virtue of the presence of these factors that treatment in hospitals is, as a rule, to be recommended in preference to treatment of the patient at home.

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ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. WILMER AND CAMPBELL

Dr. Foster Kennedy, New York: I agree decidedly with Dr. Campbell that, unless we can apply drugs in a more or less intelligent way to the pathology of the disease, we ought to rely almost entirely on physical and psychologic therapeutics. Apropos, however, of our present practice in the treatment of tabes and other syphilitic disorders of the nervous system, I should like to emphasize a position which every medical man, if placed in the position of his patient, would adopt for himself; namely, that once an individual has been definitely infected with syphilis, especially of the spinal nervous system, that patient can never be told that he has had sufficient treatment for the rest of his life. Recurrences occur too frequently to allow any such attitude as that to be adopted, and I am convinced that periodic

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treatment of the syphilitic, if neurologically syphilitic, will keep in abeyance many of the acute forms of meningitis which quite frequently occur after inadequate treatment. Luminal is the ideal sedative to be used in epilepsy and also in the neuroses associated with the menopause. In overtoned spastic cases resulting from lesions in which the pictures of severe paralysis agitans are produced, I have obtained excellent results by giving 25 minims of belladonna, three times a day, and then scopolamin (hyoscin) at night. The fact that such results can be produced by a drug would go to show that the lesion is not a fixed one, but is rather an edematous block. I support Dr. Campbell in what he said about the use of endocrine products in neurologic practice. Repair processes in central nerve lesions are so slight and so slow that in respect of them we are always in a state of therapeutic ineptitude. Consequently, we easily fall prey to wishful thinking. Too much is being claimed for the repair efficacy of glandular extracts. Many people are being deceived, and false hopes in all kinds of conditions are being aroused. People with brain tumor, etc., are constantly being told they have only to take a little pituitary extract and they will be healed. This cannot be done—yet.

Dr. Claes Julius Enebuske, Boston: Four pharmacodynamic groups were mentioned by Dr. Campbell as being used in the more frequent neurologic and psychiatric disorders, namely, hypnotics, sedatives, antispasmodics and anodynes. I miss a fifth pharmacodynamic principle, the etiotropic mode of action. The etiotropic conception is not my invention. The value of drugs in neurology is necessarily uncertain as long as the medicinal substances are known in the profession chiefly through descriptive terms of properties in vitro, and as long as their use is founded chiefly on empiricisms and inherited habits of thinking. The value of drugs in neurology attains a higher stabilization in the measure as the use of the medicinal substances is being rationalized by, principally, two processes of development: (1) the development of their application in accord with inalterable physiologic laws, for the attainment of definitely preconceived pharmacodynamic action, and (2) the development of scientific biologic tests, whereby it can be controlled that the dynamic action indicated and desired is also actually obtained. The technical realization of this development is, in the main, a biochemical problem. Great advancement in the value of certain drugs has been achieved. For instance, sodium chlorid has attained prominent value through the development of the definition of the strength of solutions in terms of gram-molecule per volume-unit and the definition of its pharmacodynamic action in terms of osmotic pressure. By the application of these principles in a case of dementia praecox—a young man who had crushed the end-phalanx and denuded the second phalanx of a finger—I obtained growth of new healthy soft tissue

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completely covering the bone and resulting in a finger as shapely and useful as before. And yet the sodium chlorid was not entirely necessary to this result. For a greater or lesser part of it might have been substituted by certain other chemicals, if only the idea of gram-molecule per volume-unit as expression of the strength of the solution and the idea of osmotic pressure as expression of its action were retained. There are other new principles, biochemic and pharmacodynamic, which are very promising for psychiatric therapy. My investigations have developed an important mode of action in relation to the cause of certain physical symptoms which occur with great frequency in psychiatric diseases, being present in practically every case of the dementia praecox group and also in the manic-depressive group.

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INTERRELATIONSHIP OF FUNCTION OF THE THYROID GLAND

AND OF ITS ACTIVE AGENT, THYROXIN, IN THE TISSUES OF THE BODY

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The highly essential function of the thyroid is the elaboration and delivery to the body of thyroxin. The gland secretes and stores in its acini the so-called colloid. It seems highly probable that the latter function is an accessory to the production and storage of thyroxin, and that in it is stored iodin for the elaboration of this agent. There is no definite evidence that the thyroid has any other function.

THYROXIN

In 1914 Kendall separated from the thyroid gland the pure chemical compound thyroxin. He proved thyroxin to be its active agent. In 1915, in attempting to correlate the available data with regard to the function of the thyroid gland and of its active agent, thyroxin, in the tissues of the body, I formulated these deductions:

1. Thyroxin is active directly or indirectly in the cells throughout the tissues of the body.
2. Thyroxin is an agent hastening the rate of formation of a quantum of potential energy available for transformation on excitation of the cell.
3. Hyperthyroidism is the physiologic status of an individual otherwise normal when the thyroxin in the tissues is sufficient to hold the basal metabolism above normal.
4. Hypothyroidism is the opposite of hyperthyroidism.
5. All the phenomena in pure hyperthyroidism are those that must attend a sustained elevation of the basal metabolism.
6. The status of the hyperfunctionating adenomatous goiter is the result of a pure hyperthyroidism.
7. The status of exophthalmic goiter is not accounted for by a pure hyperthyroidism.

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Various observations correlated on these working hypotheses led me, in 1917, without previous estimates of the basal metabolism following the administration of thyroxin, to give intravenously to a myxedematous patient, supposedly having no thyroid gland, 22 mg. of thyroxin and to anticipate the reaction which followed. The reaction was approximately the average of those obtained from several hundred doses since administered. From these studies the following deductions may be drawn:

1. After the administration of a single dose of thyroxin sufficient to bring the basal metabolism to normal, the physiologic status of a thyroidless patient becomes normal in from ten to twelve days, remains approximately normal for ten days, and returns to the preexisting status in from five to seven weeks.

2. The amount of thyroxin in the tissues (exclusive of the thyroid) of the average normal man is approximately 14 mg. Kendall, from an analysis of the iodin content in the tissues, recently estimated the amount to be 14 mg.

3. The average daily exhaustion of thyroxin in the tissues is between 0.75 and 1 mg.

4. A shift of 1 mg. of thyroxin in the tissues of the body is accompanied by a corresponding rise or fall of between 2 and 3 per cent. in the basal metabolism.

5. Fourteen milligrams of thyroxin given to a thyroidless person is not fully exhausted until from the end of the fifth to the eighth week.

Two milligrams of thyroxin a day may hold the basal metabolism from 20 to 30 per cent. above normal; 3 mg. a day may hold the basal metabolism 50 per cent. above normal.

Fifteen milligrams of thyroxin given intravenously to patients with exophthalmic goiter who have a basal metabolism above + 65 may not cause notable reaction; when given to patients having large colloid goiter with bruit, the bruit disappears and the thyroid shrinks rapidly, but constitutional reaction may be absent. With these two exceptions a sustained elevation of the basal metabolism has followed every intravenous dose of more than 1 mg. of thyroxin.

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The drop in the basal metabolism following the traumatic destruction of the entire thyroid, its resection for hyperfunctioning adenomatous goiter, the administration of a large dose of thyroxin or the withdrawal of this agent after a period of daily administration is always gradual, extending over days. These observations indicate that the thyroid under average normal conditions maintains an approximately constant level of thyroxin in the body, and that an elevation of basal metabolism of more than 5 per cent., followed within twenty-four hours by a corresponding drop, cannot, except possibly in relatively high degrees of hyperthyroidism, be attributed to fluctuation in the thyroxin content of the body.

Without knowing the exact mechanism of the normal stimulation of the thyroid we can assume that it is brought into play by a drop in the amount of thyroxin in the tissues of the body. This being true, the daily administration of 1 mg. or more of thyroxin should place the thyroid at partial or complete rest, at least so far as the production of this agent is concerned. Following this hypothesis, the daily administration of from 0.5 to 1 mg. of thyroxin to a normal person might not be attended by any general physiologic reaction. We have given a daily dose of 1 mg. to a number of persons, apparently having a normal thyroid function, for months without any deflection of the basal metabolism from the normal. There are some objections to drawing definite conclusions from these results and from other observations which indicate that the thyroid gland is placed at rest by the administration of thyroxin; however, the mass of evidence supports the hypothesis.

There are approximately 10 mg. of thyroxin in 150 grains of desiccated thyroid. The physiologic reaction following the administration of thyroxin is, so far as we have made any observation, identical with that following the administration of the fresh or desiccated

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thyroid gland containing this agent. Absorption from the intestinal tract is, however, very erratic, and desiccated thyroid cannot be given intravenously.

A daily oral dose of 1.6 mg. of thyroxin will hold the basal metabolism of most thyroidless individuals within the normal limits. In most instances the dose established two or three years ago has not had to be changed, the basal metabolism estimates being within 5 per cent. of the average normal each time the patient has returned for observation. A daily dose of from 2 to 3 mg. of thyroxin or 20 grains of desiccated thyroid given by mouth will not fluctuate the basal metabolism or cause any physiologic reaction in many patients in whom this dose given intravenously causes the quantitative reaction almost standard for myxedematous patients. In isolated cases, 250 grains of desiccated thyroid has not caused any reaction. This failure of absorption or destruction of thyroxin before reaching the general circulation is characteristic of a considerable percentage of patients who have diffuse colloid goiter and of patients in the various groups having low basal metabolism readings not attributable to a primary hypothyroidism. This failure of absorption, the difficulty of carrying out daily intravenous administration over a long period, the probability that the thyroid is placed at partial or complete rest, and evidence that under certain conditions the thyroid picks up and stores part of the thyroxin, have been most baffling in the attempt to study quantitatively the reactions of persons having functioning thyroids.

As thyroxin, other factors remaining constant, determines the rate of transformation of energy in the organism, it can be assumed that the rate of exhaustion of thyroxin for a given period is determined, to a large extent at least, by the total transformation of energy. That the rate of exhaustion relative to the total metabolism is not the same in all the organs or reactions of the organism is probable. There is much

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to suggest that the rate of exhaustion of thyroxin in the female is higher than in the male.

It seems probable that the relation of the rate of exhaustion to the total metabolism for a given period might be roughly determined by fluctuating stress on a thyroidless person whose basal metabolism has been held at normal sufficiently long to permit of readjustment of physiologic functions. We have not, up to the present, been able to control such a patient for the required time.

It is quite probable that there is a gradual adaptation downward in the thyroxin content of the tissues, and hence in the thyroid activity in some of the classifiable and unclassifiable conditions not primarily hypothyroid, with which a low basal metabolism is associated. The clearest evidence of this is the gradual adaptation downward of the basal metabolism to long continued low food intake. The term secondary hypothyroidism might, though perhaps inadvisably, be applied to such a status. That a disuse atrophy may result is possible, if not probable. Assuming that the rate of exhaustion of thyroxin in the tissues should be determined largely by the total energy transformation, and hence that disuse atrophy and inability of the thyroid to respond to a suddenly increased demand might follow a prolonged low food intake, three patients with hysterical dysphagia, who had lived and worked hard on a very limited liquid diet for a number of years, were held under observation following the sudden relief of the dysphagia and return to a normal diet. As anticipated, the basal metabolism of each patient dropped from 10 to 22 per cent. below normal in three weeks, and the edema, the skin changes, and other minor evidence of myxedema developed. This observation has added significance in the light of the following facts.

The basal metabolism of a thyroidless individual is from 30 to 40 per cent. below the average normal.

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The edema of myxedema develops, or at least becomes recognizable, when the basal metabolism drops from 15 to 17 per cent. below the average normal. In a myxedematous person having a basal metabolism ranging near this point, the edema may appear after stress, and disappear after rest. Sustained stress exhausts the thyroxin more rapidly than it can be produced by the thyroid and the basal metabolism drops a few points. A recognizable edema may disappear and reappear with a shift of 1 mg. or less of thyroxin in the tissues of the body. A drop in the basal metabolism to 40 per cent. below normal does not cause edema in the classifiable and unclassifiable conditions not due primarily to hypothyroidism. This relation of edema to the basal metabolism is of the highest significance in the differential diagnosis of primary hypothyroidism and of the other conditions with which a low metabolism is associated.

If we are right in the inference that the amount of thyroxin in the tissues of the body throughout the range of normal or near normal conditions is fairly constant, and that the rate of exhaustion is determined to a high degree by the total metabolism or fluctuations in specific metabolic reactions, the thyroid is subject to the greatest stimulation when the amount of this agent in the body is lowest, that is, when the tendency is toward hypothyroidism. This indicates that increased vascularity and histologic evidence of increased activity in the thyroid should not be accepted, without hesitation, as evidence of hyperthyroidization of the tissues of the body. This, of course, does not apply if the stimulus to the thyroid is not originating in the demands of the organism, as is probably true in pathologic conditions, such as exophthalmic goiter and hyperfunctioning adenomatous goiter.

The ease with which the phenomena attending an elevation of the metabolism and an increased rate of exhaustion of thyroxin in the tissues from stimulation

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originating in the central nervous system and the resulting evidence of stress on the thyroid may be confused with the phenomena of hyperthyroidism is apparent when we recognize that but for the transformation of part of the energy to motion, the phenomena of physical exertion and the resulting fatigue could be distinguished only with difficulty from those of pure hyperthyroidism. The phenomena of mild exophthalmic goiter are so much like the psychoneurotic manifestations due to lack of assurance that the thyroid is frequently resected for the latter condition. The lack of assurance is frequently cut out, and both the physician and patient satisfied; the latter enjoys a period of ease after demanding restitution of fees from previous consultants.

THYROID GLAND

The normal thyroid gland is constituted of acini containing colloid and lined with relatively dormant appearing cuboidal or low columnar epithelium supported by the sustentacular tissue common to gland structure. Various interpretations have been placed on the groups of cells in the stroma of the gland; however, they are not known to have any definite specific function peculiar to the thyroid.

Three departures from this somewhat conventional picture of the normal thyroid gland dominate the study of the relationships of the anatomic changes and functional activity of the thyroid, and form the basis for the classification of conditions grouped under the term goiter: (1) hypertrophy of the alveolar epithelium; (2) an increase of the intra-alveolar colloid, and (3) the development of new alveoli. On these changes, goiter may be primarily classified as hypertrophic, colloid and adenomatous.

Diffuse colloid goiter and diffuse hypertrophic goiter may be considered anatomic expressions of functional disturbance in prenatally developed thyroid acini. Ade-

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nomatous goiter is new tissue developing postnatally from the stimulation of embryonic cells. All these types may be present in the same gland. Adenomatous tissue may be either encapsulated or nonencapsulated.

Three clear-cut abnormal physiologic states are associated with anatomic changes in the thyroid: (1) pure hyperthyroidism; (2) pure hypothyroidism, and (3) exophthalmic goiter.

A definite syndrome of hyperthyroidism is, with rare exceptions, associated with diffuse hypertrophic or adenomatous goiter, or follows the administration of thyroxin.

The assumption that the status of adenomatous goiter is attributable simply to an excess of the normal thyroid product (pure hyperthyroidism) rests largely on a correlation of at least approximately accurate observations. They are:

1. The physiologic status of a thyroidless individual returns to normal when the basal metabolism is brought to normal by the administration of thyroxin.

2. The phenomena induced by the administration of thyroxin and the phenomena associated with adenomatous goiter are identical and are those that must attend a sustained elevation of the metabolism.

3. These phenomena disappear with the dropping of the basal metabolism to normal within three weeks after the enucleation of the adenoma.

The status of exophthalmic goiter, while in the main hyperthyroid, cannot be attributed wholly to an excess of the normal thyroid product. The characteristics of exophthalmic goiter may be due to an incomplete thyroxin molecule.

The capacity of the normal thyroid to elaborate thyroxin without notable histologic change is evidenced by the failure to demonstrate such changes after the resection of at least three fourths of the thyroid. That the thyroid is subject to the laws of rest and repose; that it stores thyroxin, iodin and colloid, and that during periods of stress it absorbs a portion of the

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colloid, utilizes the stored iodin, and delivers thyroxin to the blood stream; that hyperthrophy is indicative of a relatively high degree of stimulation; that intensive stimulation will cause hypertrophy and hyperfunction; and that the intracellular changes are indicative of the secretory processes of the thyroid vesicles functioning under normal conditions can be accepted with little, if any, reserve. However, several themes that pervade, if they do not dominate, the literature on the thyroid gland are open to question: (1) Hypertrophy is indicative of the production of the active agent of the thyroid in excess of the average normal; (2) the storage of colloid in excess of the normal is indicative of a resting phase of the thyroid and is a result of damage from preexisting hypertrophy and hyperplasia, and (3) the administration of iodin places the thyroid at rest.

For evident reasons we might anticipate that the administration of thyroxin to the point of supplying the demands of the organism would place the thyroid at rest and that the administration of iodin, if the supply of this element were otherwise deficient, would favor thyroid productivity.

Areas of hypertrophy, "some hypertrophy" (MacCarty), are present in such a percentage of all thyroids resected that this degree of hypertrophy has little, if any, tangible significance. In exophthalmic goiter, diffuse hyperthrophy of the thyroid is rarely absent, but even in severe cases it varies from the most marked degree to the vanishing point. Diffuse hypertrophy unassociated with a syndrome that is or is not distinguishable from that of exophthalmic goiter is present in approximately only one or two of each thousand human thyroids resected. Many patients in this group later develop frank exophthalmic goiter. That all such thyroids are a part of this complex is possible, if not probable. Whatever their significance, the incidence demonstrates that they have no relation to preg-

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nancy, to adolescence, and to the conditions supposed to throw stress on the thyroid and produce diffuse hypertrophy. On the other hand, in each thousand thyroids resected for exophthalmic goiter in patients with a high basal metabolism and moderate exophthalmos, from one to three show only pure diffuse colloid goiter. I am confident that hypertrophy was present at the time the exophthalmos developed.

The thyroids of many domestic and wild animals become markedly hypertrophic with changes such as of surroundings and diet, without any detectable constitutional disturbances. When hypertrophy is present, the findings are often more readily attributable to causes throwing stress on the thyroid than to an excess of thyroxin in the tissues. This hypertrophy can be prevented or caused to disappear by the administration of iodin. The same is true of the hypertrophic goiter of fish (Gaylord). The goiters of pig cretins are hypertrophic and the inference that they are under high stimulation is warranted. Iodin administered to the mothers prevents this type of goiter and the hypothyroidism, the immediate cause of the goiter, not the result.

The remnant of the thyroid in human cretins, if present, is usually distended with colloid. Diffuse hypertrophy is sometimes present. The nodules found in cretins usually shrink rapidly following the administration of thyroxin. Nodules 5 cm. in diameter may be reduced within three or four weeks to the point of being barely palpable. It has long been known that iodin favors the disappearance of colloid goiter. Marine has demonstrated that iodin administration prevents the development of diffuse colloid goiter in man. What may be considered the acme of diffuse colloid goiter is most prevalent from the seventeenth to the twenty-first year. Each lateral lobe may be as large as a good sized fist. The thyroid arteries are distended and

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roll under the finger like a large lead pencil; bruit and loud thrill are present, and in the majority of cases the basal metabolism is from 8 to 15 per cent. below the average normal. In from twelve to twenty-four hours following the administration of thyroxin, the thyroid vessels are not palpable, and the bruit and thrill are no longer audible. The gland rapidly shrinks in size, in some instances becoming barely palpable in three weeks. The continuous administration of thyroxin prevents the reappearance of the goiter; however, on withdrawal of the drug, the thyroid may rapidly attain its original size. After absorption of the colloid, iodin in many instances at least will prevent its redeposition. That colloid goiters are capable of producing thyroxin if sufficiently stimulated is demonstrated by the fact that the basal metabolism drops but little, if any, following a resection of the gland.

The majority of diffuse colloid goiters that have come under our observation since we have fully recognized the fallacy in the absorption of thyroid preparations have been made to disappear or become barely palpable. The thyroid of the human cretin distended with colloid reacts as does the colloid goiter of adolescences. The preceding observation on the occurrence of colloid and hypertrophic goiter and their reactions to thyroxin and iodin administration can be correlated on the hypothesis which, if correct, is essential to our understanding of the relation of functional activity to anatomic changes in the thyroid: Without definite knowledge of the exact mechanism we can assume that the normal stimulation of the thyroid is brought into play by partial exhaustion of the thyroxin in the tissues. Factors interfering with the production of this agent lower the amount delivered from the thyroid. There may be several such factors. The one known factor is an actual or relative shortage of iodin. A thyroid so handicapped, if sufficiently stimulated, can produce a normal amount or even an excessive amount

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of thyroxin; however, relative to the normally functioning gland, it tends to lag behind the demands of the tissues, that is, it does not respond quantitatively to stimulation as does the normal thyroid. The degree of stimulation of such a gland is above the average and probably increases as the thyroxin content of the tissues drops. Basal metabolism estimations suggest that this lag expressed as the amount of thyroxin in the tissues never exceeds 4 mg. The human gland acting under these conditions deposits an excess of colloid in its acini. This constitutes the diffuse colloid goiter of adolescence. Diffuse colloid considered as an entity probably never hyperfunctions. That glands of most animals acting under the same or simliar conditions develop diffuse hypertrophy seems probable.

It might be contended that the deposit of colloid interferes with the function of the thyroid and thus causes a shortage of thyroxin in the tissues. The mass of data does not correlate with this theory as it does with the theory attributing the mild hypothyroidism and colloid deposit to a common factor: namely, stimulation of the thyroid acini which are in some way handicapped in their functional ability. A hypothyroidism of sufficient degree to cause edema is, according to our observations, never due to goiter.

ADENOMATOUS GOITERS

Goiters usually classified under the terms "simple," "endemic," "adolescent," and so forth, are diffuse colloid, adenomatous, or a combination, particularly at their inception, of the two types. The majority of such goiters are first noticed during the latter half of the second decade. The colloid goiter usually disappears before the twenty-fifth year; however, there is a tendency for a thyroid once overloaded with colloid, irrespective of its functional activity, to retain more than the normal amount, that is, sufficient to make the gland easily palpable throughout life. The adeno-

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matous nodules, often during the early part of their history buried in colloid goiter, never disappear, although they fluctuate much in size with their colloid content, vascularity, and degenerative changes.

The administration of iodin may prevent the formation of colloid goiter. That it may also be almost equally efficacious in the prevention of adenomatous goiter in adolescence seems probable. In fact, if the theme here presented is correct, to control adolescent goiter means to control adenomatous goiter also.

Two theories have prevailed with regard to hyperfunctioning adenomatous goiter: first, that the adenomatous tissue elaborates and delivers an excess of thyroxin, and second, that the adenoma in some way stimulates the surrounding thyroid tissue to hyperfunction. Though the question must still be considered open, the evidence correlates best with the theory that the adenomatous tissue hyperfunctions. Irrespective of the question of which type of tissue furnishes the excess of thyroxin, there is no doubt that the adenomatous tissue actually elaborates thyroxin and stores colloid and iodin. In the following discussion of adenomatous goiter, the facts may be coordinated with either theory; however, I have assumed that the adenoma hyperfunctions.

The majority of adenomatous goiters have their inception in colloid goiter. The embryonal cells seem to be stimulated through the same mechanism that forces the postnatally developed gland to maintain a normal level of thyroxin in the tissues. Possibly we should look on adenomatous tissue as a compensatory attempt. Such a theory does not eliminate the possibility that the formation of the new tissue may in some instances be excited by local irritants. Early in its life history, new adenomatous tissue can not function. A number of observations suggest that it can elaborate and store colloid long before it can elaborate and store thyroxin. It seems more prone, as

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does the prenatally developed thyroid tissues, to store colloid if it is unable to elaborate thyroxin or the rate of stimulation of the thyroid is above the average normal. Only rarely are the factors such that the adenomatous tissue will function, at least to the point of causing hyperthyroidism, before the latter half of the third decade although, as a rule, it is palpable in the second decade of life. The average interval between the time the adenomatous goiter is first noticed and the onset of hyperthyroidism, including only those that hyperfunction before coming under observation, is seventeen and one-half years. While the normal stimulating mechanism is a factor in the inception of the adenomatous goiter, once this tissue has started to function, it does so erratically and without relation to the needs of the individual. This observation is borne out by the fact that the basal metabolism drops to normal, but not below, within eighteen days after the resection of the adenomatous tissue, and there is no tendency to a recurrence of the hyperthyroidism.

Six patients have come under my observation who, following very extensive resection of the thyroid for combined adenomatous and colloid goiter, have a basal metabolism from 12 to 17 per cent. below normal and a recurrence of multiple adenomas. These adenomas react to thyroxin as does colloid goiter. One of the patients has been under almost constant observation for two years. When the basal metabolism is brought to normal, the adenomas 5 cm. in diameter almost disappear. She can estimate her basal metabolism within 5 per cent., if it is not elevated above normal, from the size of the adenomatous nodules.

While the hyperthyroidism may come on suddenly and its course may be marked by waves of high intensity, it is characteristic of the disease to come on insidiously and for a long period, not infrequently for years, to run a course of low intensity, and to be brought to attention by the phenomena attributable to fatigue

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and by resulting degenerative changes, rather than by changes indicating a hyperthyroid state. Some patients may be hyperthyroid for many months either from hyperfunctioning adenomatous goiters or from the administration of thyroxin, and wholly unconscious of any departure from the normal status. Those of a nervous temperament, particularly the type prone to develop cardiac neuroses, are more apt to be disturbed.

The development of diffuse colloid goiter in man, other factors remaining constant, is determined by an equation taking into consideration the iodin available to the thyroid and the rate of exhaustion of thyroxin in the tissues. Infection of the organism, at least when attended with fever, probably increases the rate of exhaustion of thyroxin in the tissues. That infection of the thyroid can stimulate the gland to hyperfunction is indicated by a moderate degree of hyperthyroidism early in the history of patients having diffuse thyroiditis ultimately resulting in myxedema. That introduction of bacteria into the digestive tract is an important factor, if not the primary cause of endemic goiter, is fairly well established. As to how the organisms act in the host, there is no definite evidence. That the bacterial flora of the digestive tract may sufficiently interfere with the absorption of the small amount of iodin in the available diet is a possibility, particularly in areas in which this element is relatively small. The relation of the bacterial flora to the available iodin would well explain the geographic distribution of endemic goiter.

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FUNDAMENTAL IDEAS REGARDING BASAL METABOLISM

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As early as 1839, Sarrus and Rameaux [1] stated that, since the loss of heat in animals must be proportional to their surface area, therefore the heat production must be proportional to the same unit.

Regnault and Reiset,[2] ten years later, wrote:

> The consumption of oxygen absorbed varies greatly in different animals per unit of body weight. It is ten times greater in sparrows than in chickens. Since the different species have the same body temperature, and the smaller animals present a relatively larger area to the environmental air, they experience a substantial cooling effect, and it becomes necessary that the sources of heat production operate more energetically and that respiration increase.

Only three years after this, Bidder and Schmidt [3] made the following thoroughly modern statement:

> The extent of the respiration, like every other component of the metabolism process, is to be regarded as a function of one variable, the food taken, and one constant, a distinctly typical metabolism (Respirationsgrösse) which varies with the age and sex of the individual. This factor characterizes every animal of a given race, size, age and sex. It is just as constant and characteristic as the anatomic structure and the corresponding mechanical arrangements of the body. It is in the main determined by the heat consumption in the organism; that is to say, the replacement quota for heat lost to the body through radiation and conduction to the environment in a given unit of time. It may therefore be used to determine this, or in case the factor of heat loss is known, one can deduce the extent of the metabolism.

1. Sarrus and Rameaux: Bull. Acad. roy. de méd., Paris **3**: 1094, 1839.
2. Regnault and Reiset: Annales de chimie et de physique, Series 3 **26**: 299, 1849.
3. Bidder and Schmidt: Die Verdauungssäfte und der Stoffwechsel. Mitau and Leipzig, 1852, p. 348.

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This typical metabolism . . . is that of the fasting animal. It must be nearly the same in animals having the same body volume, surface and temperature; the larger the body surface, the body volume and temperature remaining constant, or the higher the body temperature with surface and volume constant, the higher will be the metabolism as determined by the laws of static heat.

Of course a sharp mathematical treatment of this phenomenon can be thought of only after very numerous and exact experimental determinations on animals of most varied form, size and temperature.

Rubner [4] first applied exact calculations to this problem, and he announced that dogs varying from 3 to 30 kg. in weight produced the same number of calories per square meter of body surface, though per kilogram of body substance the heat production was 88 calories per kilogram in the smallest dog and only 36 calories per kilogram in the largest one. He remarks:

Large and small dogs do not metabolize different quantities of food because their cells are differently organized, but because cooling influences on the skin excite the cells to activity.

Shortly after Rubner's publication, Richet, in 1885, showed that a cat, a rabbit and a goose, all of similar weights, produced approximately the same amounts of heat. He stated that in future one should express all calorimetric observations in terms of surface area and not in weight, a principle now very largely followed in the United States.

Rubner later came to a better understanding regarding the cause of the Law of Surface Area. He found that two guinea-pigs of different sizes had the same heat production per square meter of surface, even though they lived surrounded by air at a temperature of 30, thus excluding all thermal influences. He realized from this that the level of the basal metabolism could not be caused by the influence of cooling on the body, and no one has since thought so. Rubner,[5] however, stated that he believed that the phenomenon

4. Rubner, M.: Ztschr. f. Biol. 19: 549, 1883.
5. Rubner: Die Gesetze des Energieverbrauchs bei der Ernährung, Leipzig and Vienna, 1902, p. 174.

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observed was the result of accommodation to the action of cold to which animals in former ages had been exposed.

My own work has shown that a cold sugar solution, introduced into the stomach of a dog, can induce an extra production of heat extending over several hours. The body can therefore still respond to a withdrawal of heat by a compensatory production of it.

Rubner calculated the surface area of animals by the formula of Meeh,[6] published in 1879. This formula assumed that the surface was a function of the $\frac{2}{3}$ power of the volume. Since animals contain the same materials, weight may be substituted for volume. The result thus obtained was multiplied by a constant k which expressed the relationship of weight in kilograms to surface in square meters for a given species. For man, the formula of Meeh was $12.3\sqrt[3]{(\text{body weight})}$.[7] It may be noted here that Dreyer, Ray and Walker[7] found that the surface area, blood volume and cross sections of the aorta and of the trachea are all proportional to the $\frac{2}{3}$ power of the weight. Dreyer later concluded that the vital capacity was a simple function of the body surface. Moulton[8] found that the surface area was a two third power function of the total body nitrogen of beef cattle and, therefore, of the protoplasmic mass. This confirms the conclusion of Carl Voit that the mass of the cells and their power to oxidize materials determines the height of the metabolism. One should remember, however, in this relation the fact that in very corpulent people the heat production appears proportional to the surface area and not to the mass of protoplasm.

Using Meeh's formula, McCrudden and I,[9] in 1912, found that the basal metabolism of a dwarf was 775 calories per square meter of surface, and of two dogs

6. Meeh: Ztschr. f. Biol. **15**: 425, 1879.
7. Dreyer, Ray and Walker: Poc. Roy. Soc. Series B **86**: 39, 56, 1912-1913.
8. Moulton, C. R.: J. Biol. Chem. **24**: 299 (March) 1916.
9. McCrudden and Lusk: J. Biol. Chem. **13**: 450, 1913.

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759 and 784 calories, respectively, results which agree within 3 per cent. Comparing these with results obtained by Benedict on four men, it was found that they produced an average of 789 calories per square meter of surface. It was also pointed out that an infant 5 months old, investigated by Howland, produced 1,100 calories per square meter of surface in twenty-four hours. This accords with former observations made in 1899 by Magnus-Levy and Falk.[10]

As early as 1895, Sondén and Tigerstedt[11] pointed out that the heat production of children during the period of adolescence was relatively higher per square meter of surface than in the adult. This long-neglected scientific information was confirmed by the contributions of Murlin and of Du Bois, as well as by the extensive and valuable studies of Benedict and Talbot. About this time it was found that the food prescribed by the commonly accepted dietary standards was insufficient for the nourishment of children in the regions of occupied Belgium and blockaded Germany.

With the establishment of the calorimeter of the Russell Sage Institute of Pathology in Bellevue Hospital during the winter of 1912-1913, under the active control of Du Bois, it became absolutely necessary to seek for accurate standards with which to compare the heat production in hyperthyroidism, for example, with the heat which the patient would presumably have produced had he been perfectly well. As there was a lack of accurate data, Gephart and Du Bois[12] investigated the heat production of several normal controls, and in their preliminary work established the value of 34.7 calories per square meter of body surface per hour as representing the basal metabolism of individuals of usual shape when the surface area was calculated by the Meeh formula. Although criticism has been made

10. Magnus-Levy: Arch. f. Physiol., Supplement, 1899, p. 388.
11. Sondén, K., and Tigerstedt, R.: Skand. Arch. f. Physiol. 6: 1, 1895.
12. Gephart, F. C., and Du Bois, E. F.: The Determination of the Basal Metabolism of Normal Men and the Effect of Food, Arch. Int. Med. 15: 835 (May) 1915.

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that protoplasmic mass is the sole criterion of the intensity of metabolism, it appeared beyond the bounds of possibility to determine the protoplasmic mass in hyperthyroidism, whereas the Meeh formula furnished the most ready means then at hand of estimating the surface area. Du Bois at that time came to the conclusion that, although Meeh's formula might not accurately measure the surface area, at least the heat production was proportional to Meeh's formula.

Finally, E. F. Du Bois actually measured the surface area of several individuals, and with his cousin, Delafield Du Bois,[13] worked out a formula from the measurements obtained. He was thus able to calculate the true surface area within an average error of ± 1.5 per cent. and a maximal variation of ± 5 per cent. Meeh's formula proved to have an average inaccuracy of 16 per cent. and a maximal variation of 36 per cent., the latter being found in the obese.

The now generally used Du Bois height-weight formula for determining the surface area indicated that the measure of the basal metabolism was 40 calories per square meter per hour in men, and 7 per cent. less than this in women. Du Bois claimed an accuracy of within ± 10 per cent., but of late others have ascribed even a greater degree of accuracy to his method. His body surface formula shows that very obese women, like the one described by Means as being a "veritable pork barrel," conform to Rubner's law that the heat production of the basal metabolism is proportional to the surface area.

Following Du Bois, Benedict and Harris published a book entitled "Biometric Study of the Basal Metabolism in Man," and gave various tables for the computation of the basal metabolism. Using these tables for people of early adult life, the calculations by both methods yield essentially the same results. The average basal metabolism of three old men, as determined by

13. Du Bois, Delafield, and Du Bois, E. F.: The Measurement of the Surface Area of Man, Arch. Int. Med. 15: 868 (May) 1915.

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Benedict, was much lower than that found in six old men by Aub and Du Bois,[14] and this tends to throw doubt upon the calculations of the true basal metabolism of old men. It may, however, be added that the basal metabolism of Zuntz remained at a constant level from the age of 41 to the age of 63.

Dreyer [15] has objected to the introduction of the standing height as a factor in the calculation of the surface area on the ground that it is not a physiologic measurement, and he regards the sitting height as a more normal expression. He has evolved a formula which is based on age and weight alone. He states that this formula indicates that basal metabolism is not a simple function of body surface.

However, Dreyer calculates that the deviation between observation and calculation for Benedict's own series is, in the case of males, 5.27 per cent. by his own formula, 5.33 per cent. by Benedict's method, and 5.65 per cent. by Du Bois' method of calculation. These differences, which amount to only 0.38 per cent. at most, do not appear to be so considerable as to manifest, for one formula over the others, a readily distinguishable refinement of procedure.

Applying Dreyer's formula to the predictable metabolism of the six old men investigated by Du Bois and Aub, the average deviation from the metabolism actually measured amounts to + 2.2 per cent., whereas Benedict's formula shows a discrepancy of + 19.7 per cent. This, however, is a detail. The main facts are established. The controversy is concerning interpretations and theories.

In a recent publication Benedict [16] pens the following statement:

As a result of the critique of the body surface law presented by Harris and Benedict, we believe that the accurate measurements of body surface made possible by Du Bois may *legiti-*

14. Aub, J. C., and Du Bois, E. F.: The Basal Metabolism of Old Men, Arch. Int. Med. **19**: 823 (May) 1917.
15. Dreyer, G.: Lancet **2**: 289 (Aug. 7) 1920.
16. Benedict and Talbot: Metabolism and Growth from Birth to Puberty, Pub. 302, Carnegie Institution of Washington, 1921, p. 159.

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mately be used in a manner heretofore never practicable in metabolism experiments, *provided* that they are considered as physical measurements and with no erroneous conceptions as to the existence of a causal relationship between surface area and heat elimination.

I believe this statement to be somewhat exaggerated. I believe that the Du Bois standards for basal metabolism can be relied on, and I also believe that, though one may doubt the causal relationship between surface area and heat elimination, such doubt will not invalidate the arithmetic employed in the calculation. In making this statement I recall the words of Carl Voit, uttered regarding another matter:

> I maintain this as an incontestable fact. It is of itself so important that I question whether it is desirable to add a word of explanation. The results of a properly conducted and properly appreciated experiment can never be annulled, whereas a theory can change with the progress of science.

The establishment of a predictable basal metabolism enabled those working with the Russell Sage calorimeter to interpret the variations from the normal in many diseased conditions and has offered a method now widely accepted throughout the world for a closer clinical diagnosis of several pathologic conditions.

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THE MEASUREMENT AND STANDARDS OF BASAL METABOLISM *

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That a strenuously active man, engaged in severe muscular work, gives off heat is not surprising to any one, but it is seldom fully realized that, even with a man in complete muscular repose, such as a bedridden patient, the end-result of all the internal glandular and muscular activities incidental to the maintenance of life is *heat*. So truly is the heat output determined by the intensity of vital processes that, conversely, it may be stated that the level of vital activity may be inferred from the amount of heat produced. This caloric index of metabolic intensity is of such a transient and fugitive nature that unusually complicated technic is required for its determination, and this fact has retarded not only its use but, more especially, an appreciation of the significance of its relationship to physiologic and pathologic research. Since heat is the end-product of all vital transformations, the latter could, theoretically at least, best be measured by some method of determining directly the heat given off from the body. Such a method calls for an extremely elaborate and costly apparatus, a calorimeter, which, to be of sufficient size for measuring directly the heat production of the human body, assumes an appearance so formidable as to unnerve completely the best of hospital technicians. Fortunately, other, indirect methods for estimating heat production are available. While heat is the end-result of glandular and muscular activity, oxidative

* From the Nutrition Laboratory of the Carnegie Institution of Washington, Boston.

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processes are essential factors in these transformations. Thus, the intake of oxygen is essential to combustion, while the production of carbon dioxid makes up a very large part of the total oxidative activities of the body. Therefore, if one can measure accurately the carbon dioxid production or, still better, the oxygen consumption, a very close estimate of the total heat production, and consequently, of the end-result of the glandular and muscular activity may be secured.

COMPLICATED TECHNICS

The technics available for these measurements of the respiratory products have for many years been very complicated, involving in their most elaborate form a respiration chamber with its numerous appurtenances. In a somewhat less elaborate form, a mouthpiece or mask, together with valves and some appliance for measuring the total expired air, such as either a gas meter, a rubber bag or, more commonly, a spirometer, is necessary. But in addition to either of these forms of apparatus there is required that *rara avis,* a skilled gas analyst, on whom rests the determination of the changes in the composition of outdoor air, as it leaves the lungs. All of these methods have been in the special respiration laboratories, but have been introduced into hospitals in general to only a very small extent. Hence, clinical studies of gaseous metabolism have been made only by the relatively few workers in special laboratories, who have in but few instances been simultaneously clinicians.

A SIMPLE TECHNIC

The Nutrition Laboratory has for many years been involved in a study to simplify the costly experimental technic for the measurement of gaseous metabolism. The final outcome of this study has been the development of a portable respiration apparatus that measures with extreme accuracy and great rapidity the oxygen

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consumption of human beings. Based on the important observation that when a human subject breathes pure oxygen the amount of oxygen taken up by the blood is the same as when ordinary air is inspired, a relatively simple technic for the measurement of the oxygen consumption of man, involving neither respiration chamber, valves, weighings nor gas analyst, has been evolved. Of the two respiratory gases, oxygen and carbon dioxid, this apparatus measures the oxygen consumption alone. But since it is the common experience of all clinics that, in those experiments in which where, by the older methods, both carbon dioxid and oxygen are determined, the oxygen consumption alone is of prime significance in the vast majority of pathologic cases, it can be seen that a method restricted to oxygen determinations will supply the needs for a large series of pathologic problems.

Normal control experiments, which are a necessary feature preliminary to all studies in disease, may, with the wide distribution of the portable respiration apparatus, be of great service to physiology and, ultimately, to pathology, provided such tests are intelligently planned and skilfully carried out. Indeed, the optimist can properly take the ground that whatever faults may arise in studying pathologic cases, whatever misinterpretations of data may be made, the development and wide distribution of the respiration apparatus can be fully justified by the contributions that each user of the apparatus can rightly be expected to make to our knowledge of normal metabolism.

REQUISITE CONDITIONS

In basal metabolism measurements, the requirements are that the subject should be, first of all, in the post-absorptive condition, that is, at least twelve hours after the last meal, and secondly, that he should be in complete muscular repose, preferably lying quietly without conversation or any psychic excitement for a half

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hour before the test begins. The room temperature should be not far from 20 C., and the subject should be sufficiently clothed or covered with bedding, to be perfectly comfortable. It is our custom in the Nutrition Laboratory, in order to rule out the possibility of a slightly febrile condition, to note the buccal temperature during the period of preliminary repose. Every effort should be made to secure a series of pulse rate records. This measurement may be taken at the wrist during the actual experiment itself and during the preliminary period, but is better taken by means of ear pieces attached to a Bowles stethoscope resting over the apex beat of the heart.

To be fully comparable with previous work, all normal experiments must be so conducted as to recognize certain fundamental points. Not infrequently the value of earlier work is greatly vitiated by the absence of certain fundamental physiologic measurements. For instance, a record of the sex, age, nude weight, and the height without shoes, must be considered as an essential part of the report. In addition, since it should be the aim of modern experimenters to secure better data, it is not unreasonable to ask that two new measurements, of value in determining the nutritional state of a subject, be supplied. One of these is the sitting height, the importance of which has recently been emphasized so strongly by Dreyer [1] of Oxford and by von Pirquet's [2] use of it in the nutritional tragedy in Vienna. Furthermore, it is believed by Dr. C. B. Davenport that the investigator, at the moment of obtaining the sitting height, should also measure the sitting height to the suprasternal notch, i. e., eliminating the length of neck and head, as this additional evidence will prove of even greater value in later years. Finally, as a part of

1. Dreyer, Georges, and Hanson, G. F.: The Assessment of Physical Fitness, London, Cassell & Co., 1920.
2. Von Pirquet: System der Ernährung, Berlin, 1917, 1: 48, ff.

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the records of all those having a portable respiration apparatus at hand, with its carefully calibrated spirometer, there may reasonably be expected a measure of the vital capacity, which has also been emphasized by Dreyer [3] and by Peabody.[4]

ACCURATE MEASUREMENTS

Moreover, operators should be careful to record the degree of drowsiness of the subject. When the mouthpiece is used, unless the jaw is very much relaxed and opened, accurate oxygen measurements can readily be made with the portable respiration apparatus, and thus the question of sleepiness will not affect the technic. Parenthetically, I should like to add that a new procedure has recently been tested out in the Nutrition Laboratory, which serves admirably as a proof of absence of leak in these mouthpiece tests. Ordinarily the readings on the millimeter scale connected with the spirometer bell are taken only at the beginning and the end of a ten-minute period. In addition to these regular readings, as mentioned in various articles describing our technic,[5] it is now our custom to take a reading at about the middle of the period, say after four or five minutes, and immediately thereafter we place on top of the spirometer bell a weight, of usually not far from 35 to 40 gm. This weight remains on the bell until just before the final readings. Oviously, if there is a leak around the mouthpiece or any part of the apparatus, the weight on the spirometer bell will result in the expulsion of air from the apparatus into the room, thus indicating a larger oxygen consumption. Consequently, by computing the oxygen consumption during the first five minutes and comparing it with that

3. Dreyer, Georges: Lancet **1**: 365 (March 10) 1917.
4. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration, IV, The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch. Int. Med. **20**: 443 (Sept.) 1917.
5. Benedict, F. G.: Boston M. & S. J. **178**: 667, 1913. Hendry, M. F.; Carpenter, T. M., and Emmes, L. E.: Ibid. **181**: 285, 334, 368 (Sept. 4) 1919. Benedict, F. G.: Ibid. **182**: 243 (March 4) 1920. Benedict, F. G., and Collins, W. E.: Ibid. **183**: 449 (Oct. 14) 1920.

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during the last five minutes, one can invariably detect the presence of a leak.

Still better, if one attaches a small writing point to the counterpoise weight of the spirometer bell and allows this to write over the surface of a smoked paper kymograph drum, a remarkably satisfactory picture of the entire respiratory process can be obtained from the beginning to the end of a test. The straight line curve, touching the points representing the end of each expiration, shows a general upward tendency as oxygen is consumed, and the bell descends, and forms an angle with the base-line of the kymograph paper, varying by only two factors, first, the rate of speed of the kymograph and, second, the rate of absorption of the oxygen. Assuming that these two factors remain essentially constant throughout a ten-minute period, we can see that if there is a leak when the weight is on the spirometer bell, the last half of the curve will have a decidedly different angle. Thus it is possible by either of two methods to detect absolutely the presence of a leak, particularly in experiments during sleep. When the subject is awake, our own experience has been that it is very difficult to secure a leak around the mouthpiece. For all of our research work the graphic method is invariably employed.

If these precautions are observed, records of basal metabolism are readily made, and the difficulty then shifts from the experimental technic to the scientific interpretation of the results.

INTERPRETATION OF RESULTS

The simplification of the technic for determining the respiratory metabolism is justifiable on the grounds that such technic in the hands of well-trained men will enable a much larger and more accurate accumulation of scientific data. The simplification of such technic is, on the other hand, dangerous, when it makes

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it possible for the tyro to secure measurements, which frequently neither he nor any of his associates are in a position to interpret intelligently and from which it is possible for him to draw deductions that are not only erroneous but, since they, not infrequently, may influence for or against operative procedure, may actually be of serious harm. This rapid and accurate method makes general use of gaseous metabolism measurements justifiable, therefore, only with the proviso that the operators have, first, acquired carefully and intelligently a relatively simple technic, and secondly, that in attempting to analyze or utilize results, they have previously made an intense study of the significance of respiratory metabolism. Unfortunately, the intellectual training of the operator has by no means progressed so rapidly as has the simplification of technic; and today we face a situation in which manufacturers are ready to supply almost unlimited numbers of simplified respiration apparatus, which are in a too great number of instances secured and put to use by operators wholly lacking in this fundamental and important education.

Even the most skilled and most experienced clinicians make at times sorry exhibits of their use of apparatus of this type. The apparatus is simple to use. We believe that an intelligent high-school girl can, after a few days of training, secure most satisfactory measurements of the oxygen consumption. No effort of the Nutrition Laboratory can, however, make up for the deficiency of theoretical consideration of the significance of basal metabolism measurements on the part of the user of these readily acquired metabolism measurements.

STANDARDS OF ANALYSIS

At the very start the results obtained in suspected cases must be scanned with an idea as to their normality or their relationships to normal results, and immediately great diversity of opinion arises as to

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what is normal. It must be realized that thus far the total number of published results for normal individuals, measured by perfectly comparable technics, is only in the hundreds. From these data, a large proportion of which has been accumulated in the Nutrition Laboratory, at least three sets of standards have been proposed: (1) the earliest, by Aub and Du Bois;[6] (2) the more complete biometric analysis by Harris and Benedict;[7] (3) and more recently a subsequent analysis by Dreyer[8] of Oxford. While in general these standards agree very well among one another, as is to be supposed, since they are all drawn from practically the same material, at times marked discrepancies are noted.

Muscular activity, digestion, psychic excitement, and sleep profoundly affect the metabolism, but the modern definition of basal metabolism presupposes measurements during complete muscular repose and with the subject in the postabsorptive condition. Yet, even under these conditions, as the careful biometric analysis of the Nutrition Laboratory material shows,[7] basal metabolism is affected independently by weight, height, age and sex. The prediction of the most probable basal metabolism of any given individual can, therefore, according to Harris and Benedict, be made by the use of the two following planar equations:

For men ..... $h = +\ 66.4730 + 13.7516w + 5.0033s - 6.7550a$
For women ..... $h = +\ 655.0955 + 9.5634w + 1.8496s - 4.6756a$

where h = total heat-production per twenty-four hours, w = weight in kilograms, s = stature in centimeters, and a = age in years. To simplify the use of these equations, tables have been prepared, from which two sets of values can be drawn, added together, and the predicted metabolism obtained. These tables, as well as all of the standards previously mentioned, and other tables of data, together with illustrative computations,

6. Aub, J. C., and Du Bois, E. F.: Metabolism of Old Men, Arch. Int. Med. 19: 831 (May) 1917.
7. Harris and Benedict: Pub. 279, Carnegie Inst., Washington, 1919.
8. Dreyer, Georges: Lancet 2: 290 (Aug. 7) 1920.

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have recently been published by Dr. Thorne M. Carpenter of the Nutrition Laboratory.[9]

VARIATIONS FROM THE STANDARD

Between the ages of 20 and 40 years, within which age range most of the experimental data analyzed by Harris and Benedict were obtained, the error of prediction of the basal metabolism is the smallest. Outside of this range, however, predictions can be made only with great care. Finally, special attention should be called to the fact that the prediction of the basal metabolism of women cannot be made with anything like the accuracy obtainable with man, and that even among so-called "normal" individuals, the measured basal metabolism frequently varies greatly from the standards. For the present, persons who are "presumably in good health" are taken as "normal" individuals.

There are a great many people who are fat, who have no demonstrable pathologic lesion. There are seemingly a large number of individuals who are thin, who come under the same head. These are classified as people "presumably in good health." Much more data on normals are imperatively needed.

UNDERNUTRITION

To the factors known to influence basal metabolism, already mentioned, should be added the very important one of undernutrition. By this is meant not simply starvation, but prolonged, persistent undernutrition, which results in perhaps even greater disturbances to metabolism than does a relatively short, complete withdrawal of food. Since it is recognized that in many pathologic cases undernutrition is an ever present factor, it is readily seen how complicated the interpretation of metabolism data may become. For example, are we to consider as normal or not the thin, emaciated,

9. Carpenter, T. M.: Pub. 303, Carnegie Inst., Washington, 1921.

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16-year old girl who has a metabolism per square meter of body surface as high as that called for by the standard of Aub and Du Bois? The very fact that there is emaciation and undernutrition would speak for a low metabolism. On the other hand, if the metabolism is found to be normal by this standard, should not one suspect the presence of some superimposed factor which more than offsets the depressing influence of the undernutrition?

CONCLUSIONS

Keeping these several factors in mind, we can see, therefore, that the use of a so-called "standard" or "normal" metabolism is fraught with considerable danger and that the interpretation of metabolism results is not a simple rule-of-thumb procedure. In fact, the interpretation of results now far exceeds in complexity the actual laboratory technic. The technical stumbling blocks to the advancement of metabolism studies in clinical medicine have, we believe, been overcome. The great intellectual stumbling block, namely, lack of education with regard to the significance of metabolism measurements, cannot be overcome by the efforts of any one laboratory, one school, or one teacher. Before using gaseous metabolism measurements, it behooves every physician to familiarize himself thoroughly with the fundamentals of gaseous metabolism and its significance. May we not hope that medical schools in general will give this fact recognition and provide for it in their curriculums, thus furthering the admirable work instituted by Dr. Eugene F. Du Bois at the Cornell University Medical College.

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THE BASAL METABOLIC RATE IN HYPERTHYROIDISM

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By the term hyperthyroidism is meant the clinical syndrome resulting from the presence in the body of an excess of thyroxin, which Kendall [1] has identified as the active principle of the thyroid gland, and which, according to Plummer,[2] "is a catalyst that accelerates the rate of formation of a quantum of potential energy in the cells of the organism." This syndrome is characterized by an increased basal metabolic rate, and by intoxication clinically evidenced by nervousness, tremor, tachycardia, loss in strength and weight, and in the later stages, myocardial disintegration.

FACTORS INFLUENCING BASAL METABOLIC RATE

Plummer [2] has proved the calorogenetic action [3] of thyroxin by extensive basal metabolic rate studies, following its intravenous injection in myxedematous and normal persons, and also by partial removal of the thyroid gland from patients with hyperthyroidism. From the basal metabolic rate curves thus obtained it can be calculated that from 12 to 14 mg. of active thyroxin must be present in the body to maintain the basal metabolic rate at the normal level, and that the rate of loss or destruction of the thyroxin is probably

1. Kendall, E. C.: Isolation of the Iodine Compound Which Occurs in the Thyroid, J. Biol. Chem. 39: 125-146 (Aug.) 1919.
2. Plummer, H. S., and Boothby, W. M.: Specific Dynamic Action of Thyroxin, Am. J. Physiol. 55: 295-296, 1921.
3. Dr. Graham Lusk has requested that the term "specific dynamic action," previously used by Plummer and Boothby to indicate the calorific or heat producing power of thyroxin and epinephrin, be reserved to express the increase in heat production following the ingestion of a food-stuff, maintaining the sense of the term as originated by Rubner. The term "calorogenetic action" has been suggested by Dr. Lusk, after consultation with Dr. Francis G. Benedict, to signify the specific stimulus to metabolism given by such substances as thyroxin and epinephrin.

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not far from 0.5 mg., daily. The average calorogenetic action resulting from the intravenous injection of different amounts of thyroxin in sixty-nine cases of myxedema or hypothyroidism of varying degrees of intensity is summarized in Table 1, and a characteristic curve is given in Chart 1, together with a curve illustrating the return to normal in the basal metabolic rate, following the removal of an adenoma from a patient having adenoma with hyperthyroidism.

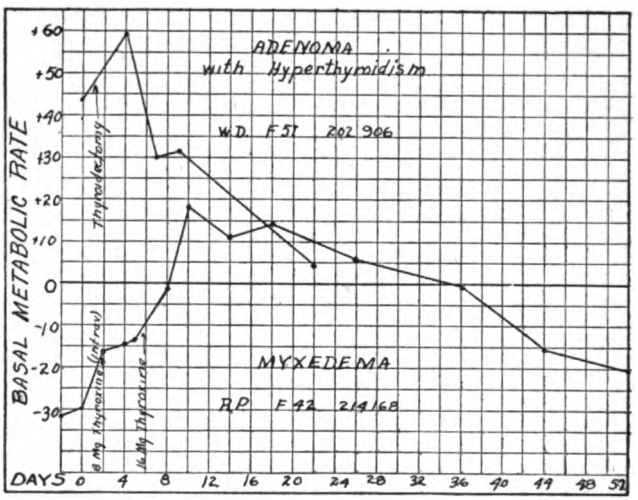

Chart 1.—On the upper curve the basal metabolic rates of a patient having adenoma with hyperthyroidism are plotted showing the original preoperative rate and the immediate postoperative rise in the metabolic rate, followed by the drop to normal after partial thyroidectomy. The lower curve illustrates the effect on the metabolic rate of a myxedematous patient of two intravenous injections of 8 and 16 mg. of thyroxin, from which can be calculated the amount of thyroxin needed to bring such a patient to a normal metabolic rate; and therefore the presumable amount of thyroxin in the body, and also the rate at which the thyroxin is destroyed or eliminated.

Therefore, pathologic variations in the basal metabolic rate are due, at least in disorders of the thyroid gland, either to an increase or to a decrease in the normal quantity of thyroxin in the body, thus explaining the characteristic and fundamental alterations in the basal metabolic rate found in hyperthyroidism and in hypothyroidism.

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However, other factors than the quantity of thyroxin in the tissues may exist which play a part in the maintenance of the normal basal metabolic rate and influence its abnormal fluctuations, especially of a temporary nature. Removal of the suprarenals has been shown by Aub [4] to cause a decrease in the basal metabolic rate, which may be brought back to normal by the slow intravenous injection of suprarenal extract, at the rate stated by Stewart and Rogoff to be the normal output in the body. Conversely, Boothby and

TABLE 1.—INCREASE IN BASAL METABOLIC RATE FROM INTRAVENOUS INJECTION OF THYROXIN

Increase per mg. 2.8	Increase per mg. per sq.m. 4.7
Average variation..... 0.7 = 25%	Average variation..... 1.1 = 23%
Largest + variation... 2.8 = 100%	Largest + variation.... 2.9 = 60%
Largest — variation... 1.8 = 64%	Largest — variation.... 2.9 = 60%

	Variation in Calorogenetic Action Depending on the Original Level of the B. M. R.				Variation in Calorogenetic Action Depending on Size of Dose			
Average B. M. R.	Average Dose	Increase per Milligram	Average Dose per Sq. M.	Increase per Milligram per Sq. M.	Average Dose	Increase per Milligram	Average Dose per Sq. M.	Increase per Milligram per Sq. M.
Above to —14	8.7	3.3	5.7	5.0	4.8	3.5	3.6	5.0
—15 to —19	9.1	2.3	5.1	3.9	6.9	2.8	5.2	5.0
—20 to —24	7.3	2.9	4.6	4.6	8.8	2.9	7.0	5.2
—25 to —29	10.9	2.8	6.2	5.0	11.2	3.3	9.3	4.8
—30 to —34	14.8	2.9	9.2	4.9	16.0	2.6	11.5	2.7
—35 and below	15.5	3.0	8.6	5.1	24.0	1.6	13.2	3.0

Sandiford [5] have shown that epinephrin possesses a calorogenetic action in man when injected subcutaneously (0.5 c.c. of 1:1,000). However, the evidence is not yet conclusive that the suprarenal glands are concerned with the normal rate of resting cellular combustion, or that they are the primary cause of abnormal rates of any definite clinical syndrome, notwithstanding the fact that decreased rates have been reported in Addison's disease and following experimental suprarenalectomy.

4. Aub, J. C.; Forman, J., and Bright, E. M.: The Effect of Adrenalectomy Upon the Total Metabolism of the Cat, Am. J. Physiol. **55**: 293, 1921.

5. Boothby, W. M., and Sandiford, Irene: The Relationship of the Increase in Blood Sugar Concentration to the Specific Dynamic Action of Glucose and to the Specific Dynamic Action of Adrenaline, Am. J. Physiol. **55**: 293-294, 1921.

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The possible increased basal metabolic rate in active acromegaly, and the decreased rate in the syndrome known as hypopituitarism, suggest that alterations in the activity of the pituitary gland may change the metabolic level. There is, however, as yet little evidence that the secretion of any part of the pituitary gland is concerned with the normal rate of cellular combustion in the sense that it acts as a calorogenetic agent. There are certain other diseases in which very occasionally an increased basal metabolic rate has been found; the cause of the increased heat production in these instances is not known.

At this meeting Du Bois has shown that the increase in the basal metabolic rate accompanying febrile diseases follows Van't Hoff's law of the velocity of chemical reactions with temperature changes; it is about doubled for an increase of 10 degrees C.

A decrease in the basal metabolic rate is characteristic of myxedema and is due to the inability of the thyroid gland to supply a sufficient amount of thyroxin. A lowered basal metabolic rate has been consistently found in experiments in prolonged fasting, and in clinical conditions of inanition in which the food supply is decreased over a long period (stricture of the esophagus, cardiospasm, anorexia nervosa, etc.); the mechanism producing this decreased rate is not known, yet it seems quite probable that it may be a compensatory slowing down of the life processes in an endeavor on the part of the organism to prolong life on a minimum utilization of its stored food, and that the thyroid gland itself takes part in this decreased compensatory process, with a consequent reduction in the amount of thyroxin acting as a catalyst.

UNSTABLE FOUNDATION OF ENDOCRINOLOGY

While we recognize that there is a biologic interdependence not only of every organ but of every cell in the body, nevertheless we are able to measure quantitatively only the calorogenetic power of the active prin-

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ciple of the thyroid gland; consequently we deprecate the tendency so much in evidence in current literature to parcel out to each ductless gland a certain definite yet entirely hypothetic power, and to build on such an unstable foundation the mammoth superstructure expressed in the term endocrinology.

ADENOMA WITH HYPERTHYROIDISM

Plummer [2] has shown that pure hyperthyroidism can be produced in a person by the administration of an excess of thyroxin, and that the syndrome thus produced cannot be distinguished from that caused by an overactive adenoma of the thyroid gland. In each case, either the discontinuance of the thyroxin or the operative removal of the adenoma ends the syndrome, and the patient rapidly returns to a normal condition, with a normal basal metabolic rate (Table 5). The characteristic symptoms of adenoma with hyperthyroidism are those that can be predicted from a knowledge of physiologic effects produced by a prolonged increase in the rate of cellular combustion; consequently, for many years Plummer [6] has spoken of the overfunctioning adenoma of the thyroid as "adenoma with hyperthyroidism," and has recognized the disease as a clinical entity with a characteristic course and symptoms. In this condition, the thyroid gland presents, on pathologic examination, discrete, single or multiple nodular adenomatous tumors in various stages of degeneration, surrounded by a definite capsule.

EXOPHTHALMIC GOITER

Until recently, adenoma with hyperthyroidism has been confused with exophthalmic goiter, which is another pathologic condition of the thyroid gland, consisting of diffuse parenchymatous hypertrophy, symmetrically involving the entire gland. Clinically, exophthalmic goiter, like adenoma with hyperthyroid-

6. Plummer, H. S.: The Clinical and Pathologic Relationship of Hyperplastic and Nonhyperplastic Goiter, J. A. M. A. 61: 650-651 (Aug. 30) 1913.

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ism, is characterized by an increased basal metabolic rate and, therefore, both diseases have in common the symptoms due to the increased rate. However, exophthalmic goiter has a different clinical course from adenoma with hyperthyroidism, and, in addition, certain peculiar and characteristic symptoms, one or more of which are present in varying degrees, such as exophthalmos, thrills and bruit, tendency to gastrointestinal crises, and a peculiar type of nervousness.

TABLE 2.—STATISTICAL STUDY OF 1,656 CASES OF GOITER*

	Adenoma		Exophthalmic Goiter		
	Non-Toxic	Toxic	Two Ligations, Rest and Thyroidectomy	One Ligation Thyroidectomy	Thyroidectomy
Number of cases studied....	254	366	341	275	420
Age	44	48	37	38	36
Duration goiter, years.....	15.7	18.0	3.4	3.9	5.0
Age at onset of goiter.....	28	30	34	34	31
Duration symptoms, years..	...	1.8†	1.6	1.5	1.8
Age at onset of symptoms..	...	46	35	37	35
Cardiac decompensation:					
Positive	13%	46%	54%	48%	24%
Probable	5%	10%	9%	5%	7%
Exophthalmos	2%‡	8%‡	67%	65%	51%
Thrills	4%	5%	63%	58%	39%
Bruit	12%	12%	87%	86%	67%
Weight, pathologic specimen, gm.	187	152	59	55	51
Glycosuria	1%	2%	1.4%	1%	1%
Blood pressure:					
Systolic (floor) §	141	158	150	146	141
Diastolic (floor)	85	86	75	74	77
Pulse pressure (floor)....	56	72	75	72	64
Pulse rate (floor).....	91	107	125	121	118
Basal metabolic rate.....	+2%	+30%	+65%	+58%	+38%
Clinical diagnosis correct**..	98%	88%	99%	98%	97%

* Differential diagnosis of adenoma without hyperthyroidism (nontoxic adenoma), adenoma with hyperthyroidism (toxic adenoma), and exophthalmic goiter. The cases of exophthalmic goiter are divided into three groups depending on the surgical treatment: (1) two ligations, two to three months' rest at home and thyroidectomy, (2) one superior pole ligation followed by thyroidectomy and (3) primary thyroidectomy.

† 1.8 represents the average duration since the onset of definite symptoms; however, it is possible to elicit a history of possible duration of 8.2 years, and in this respect differs from exophthalmic goiter which has a much clearer cut onset.

‡ The exophthalmos was only slight in these cases; never more than degree 1 on a scale of 4 and corresponds to that so frequently seen in certain types of nephritis.

§ The blood pressures and pulse rate were those obtained at the time of the clinical examination with the patient sitting.

** Accepting the report of the Section on Surgical Pathology made by fresh frozen section examination at the time of operation as correct, the previous clinical diagnosis was found to correspond as indicated. The close agreement between the pathologist's diagnosis of adenoma on the one hand and diffuse parenchymatous hypertrophy (exophthalmic goiter) on the other hand and the respective clinical diagnoses is very striking; the pathologist, however, cannot distinguish adenomas that produce hyperthyroidism from those that do not.

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That we are dealing with two entirely distinct diseases in exophthalmic goiter and in adenoma with hyperthyroidism has been proved beyond reasonable doubt by Plummer,[7] by the difference in the mode of onset of the two diseases, the clinical course and duration of the symptoms, the physical findings, and, finally, the difference in the pathology of the thyroid gland. The differential points in the two diseases are strikingly shown in Tables 2, 3 and 4. To account for these differences, the most probable hypothesis is that in exophthalmic

TABLE 3.—DURATION OF GOITER IN ADENOMA WITH AND WITHOUT HYPERTHYROIDISM AND IN EXOPHTHALMIC GOITER (1,656 CASES)

Duration, Years	Exophthalmic Goiter, per Cent.	Adenoma: With Hyperthyroidism, per Cent.	Adenoma: Without Hyperthyroidism, per Cent.
From 0 to 0.9.....	42		
From 1 to 1.9.....	15		
From 2 to 2.9.....	9 (75)	17	10
From 3 to 3.9.....	6		
From 4 to 4.9.....	3		
From 5 to 9.9.....	11	14	18
From 10 to 14.9.....	4	13	17
From 15 to 19.9.....	4	13	18
20+.....	5	43	37
Average duration, years	4.2	18	15.7

goiter, not only are the thyroid cells producing an excess of thyroid hormone, but also the secretion so formed has some abnormal and peculiar chemical properties that produce the symptoms that differentiate it from pure hyperthyroidism. Kendall [1] has suggested that probably there is, in exophthalmic goiter, a slight alteration in the structure of the thyroxin molecule.

The delay in the recognition of adenoma with hyperthyroidism as a disease distinct from exophthalmic goiter has been due in part to the fact that it was not at first recognized that small isolated areas of hypertrophic cells, such as may be found in some adenomatous thyroids, do not produce the clinical syndrome

7. Plummer, H. S.: The Clinical and Pathologic Relationship of Simple and Exophthalmic Goiter, Am. J. M. Sc. **146**: 790-796, 1913.

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of exophthalmic goiter and, conversely, that diffuse parenchymatous hyperthrophy may develop in a gland in which adenomatous tumors are incidentally present.

OPERATIVE PROCEDURE IN THE TWO DISEASES

Aside from the academic interest in differentiating adenoma with hyperthyroidism and exophthalmic goiter, the correct diagnosis is of great clinical importance because the times of onset, duration, course and outcome are different; furthermore, the operative pro-

TABLE 4.—AGE AND OCCURRENCE OF ADENOMA WITH AND WITHOUT HYPERTHYROIDISM AND EXOPHTHALMIC GOITER

Age	Percentage of Patients by Decades Having Hyperthyroidism Caused by (1) Adenoma or (2) Exophthalmic Goiter: Number of Cases	Adenoma, Toxic	Exophthalmic Goiter	Percentage of Cases in Each Decade of (1) Adenoma Without Hyperthyroidism, (2) Adenoma With Hyperthyroidism, (3) Exophthalmic Goiter: Adenoma, Nontoxic	Adenoma, Toxic	Exophthalmic Goiter
From 0 to 9	1	0%	100%	0%	0%	1%
From 10 to 19	59	8%	92%	1.5%	1%	5%
From 20 to 29	280	10%	90%	8%	8%	24%
From 30 to 39	374	13%	87%	24%	13%	31%
Below 40.....	714	....	....	33%	22%	61%
From 40 to 49	358	30%	70%	33%	29%	24%
From 50 to 59	253	46%	54%	27%	32%	13%
From 60 to 69	75	77%	23%	6%	16%	2%
From 70 to 79	2	100%	0%	0.5%	1%	0%
Above 40.....	688	....	....	67%	78%	39%
No. cases	1,402	366	1,036	254	366	1,036
Aver. age	.....	48	37	44	48	37

gram is not the same in these two diseases. In adenoma with hyperthyroidism, the operation is directed to the removal of the tumor, while in exophthalmic goiter the surgical procedures are planned to reduce, in the severer cases, the overactivity of the diffuse parenchymatous hypertrophied thyroid by successive steps: first, hot water injection, second, one or more ligations, and, finally, one or more partial thyroidectomies. In adenoma with hyperthyroidism, preliminary ligation of the blood vessels is seldom of benefit

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even in the severe cases, while in exophthalmic goiter the benefit from ligation is usually quite marked. Simple enucleation of the adenoma is almost invariably sufficient to cure the patient suffering from adenoma with hyperthyroidism; on the other hand, extensive resection of the greater part of both lobes and the isthmus is necessary to reduce the activity of the hypertrophic parenchymatous thyroid of exophthalmic goiter within normal limits, and not infrequently a second and occasionally a third resection are necessary before the intensity of the intoxication is brought within the bounds of safety. The effect of operative treatment is illustrated in Table 5.

It is well known that the course of exophthalmic goiter proceeds in cycles of intensity with intervening periods of partial and occasionally total remission. Experience has shown that the dangers of any operative interference during the rising curve of intensity and at the peak, especially if associated with gastrointestinal crises and loss of weight, are greater than during the stage of improvement. The curve of the basal metabolic rate in conjunction with the loss or gain in body weight of the patient are valuable mathematical expressions of the intensity and phase of the intoxication cycle. We have been unable to prove that the roentgen ray definitely influences the natural course of exophthalmic goiter.

DIAGNOSTIC VALUE OF BASAL METABOLIC RATE

Accepting the definition of hyperthyroidism as a clinical syndrome resulting from the presence in the body of an excess of thyroxin which increases the rate formation, and the conception tha tthe basal metabolic rate serves as a fundamental classificacation of disease,[8] it is obvious that a very sharp distinction can be drawn between mild cases of

8. Boothby, W. M.: The Fundamental Classification of Disease by the Basal Metabolic Rate, J. A. M. A. 76: 84 (Jan. 8) 1921.

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exophthalmic goiter, and those conditions known as "effort syndrome," "disordered action of the heart," "cardiac neurosis," "nervous instability," "neurocirculatory asthenia" or "neurasthenia," which on superficial examination present some of the signs and symptoms of mild exophthalmic goiter, but in which the basal metabolic rate is normal, and which on close analysis can be shown not to be dependent on an excess in the body of the thyroid hormone. The basal metabolic rate is of particular diagnostic value in these cases when they are accompanied, apparently without causal relationship, by a colloid enlargement of the thyroid gland as so often occurs in the regions of endemic goiter.

VALUE OF VARIOUS TESTS

Confusion in the differential diagnosis of functional neurasthenia from mild exopthalmic goiter and adenoma with hyperthyroidism has been increased during the last few years by the revival of the epinephrin hypersensitive test in a new guise by Goetsch.[9] A series of studies by Peabody [10] and his associates, and similar studies from our laboratory,[11] have shown that there is no correlation between the intensity of the epinephrin reaction and the degree of hyperthyroidism as controlled by simultaneous studies of the basal metabolic rate; also, that the so called "positive" epinephrin reaction is present in a large percentage of cases that are not hyperthyroid, and even occasionally in patients with myxedema. Studies on the action of epinephrin by Boothby and Sandiford [12] show that

9. Goetsch, E.: Studies on Disorders of the Thyroid Gland: Hypersensitiveness Test with Especial Reference to "Diffuse Adenomatosis" of the Thyroid Gland, Endocrinology **4**: 389-402 (July-Sept.) 1920.

10. Peabody, F. W.; Sturgis, C. C.; Tompkins, E. H., and Wearn, J. T.: Epinephrin Hypersensitiveness and Its Relation to Hyperthyroidism, Am. J. M. Sc. **161**: 508-517, 1921.

11. Boothby, W. M.: Adenoma of the Thyroid with Hyperthyroidism (Thyrotoxic Adenoma), History of the Recognition of This Disease as a Clinical Entity: A Study of the Symptomatology with Basal Metabolic Rates, Endocrinology **5**: 1-20 (Jan.) 1921.

12. Boothby, W. M., and Sandiford, Irene: The Effect of the Subcutaneous Injection of Adrenalin Chlorid on the Heat Production, Blood Pressure and Pulse Rate in Man, Am. J. Physiol. **51**: 200-201, 1920.

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TABLE 5.—EFFECT OF OPERATIVE TREATMENT ON 284 CASES OF EXOPHTHALMIC GOITER AND ADENOMA

	Exophthalmic Goiter								Adenoma			
	Two Ligations, at Home and Thyroidectomy				One Ligation and Thyroidectomy			Primary Thyroidectomy		With Hyperthyroidism		Without Hyperthyroidism	
	Before Treatment	Ten Days After Second Ligation	After Two Months' Rest	After Thyroidectomy	Before Treatment	Ten Days After First Ligation	After Thyroidectomy	Before Treatment	After Thyroidectomy	Before Treatment	After Thyroidectomy	Before Treatment	After Thyroidectomy
B. M. R.	+68%	+51%	+43%	+20%	+60%	+39%	+17%	+36%	+8%	+35%	+6%	—8%	—9%
Systolic blood pressure	139	132	131	125	137	126	119	133	122	145	138	115	115
Diastolic blood pressure	75	72	72	75	71	66	71	73	73	81	78	74	70
Pulse pressure	64	60	59	50	66	60	48	60	49	64	55	41	45
Pulse rate	122	114	108	98	116	106	92	107	86	102	79	74	73
Weight	52.3	48.0	56.6	56.3	52.8	49.7	50.7	53.3	52.9				
No. cases in each group	55				42			72		92		23	

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there is not sufficient physiologic basis for the assumption that the reaction to the subcutaneous injection of an active principle of the suprarenal gland is indicative in clinical medicine of activity of the thyroid gland. The blood sugar curves as shown in Chart 2, following the ingestion of 100 gm. of glucose, have not been sufficiently consistent in the different types of cases

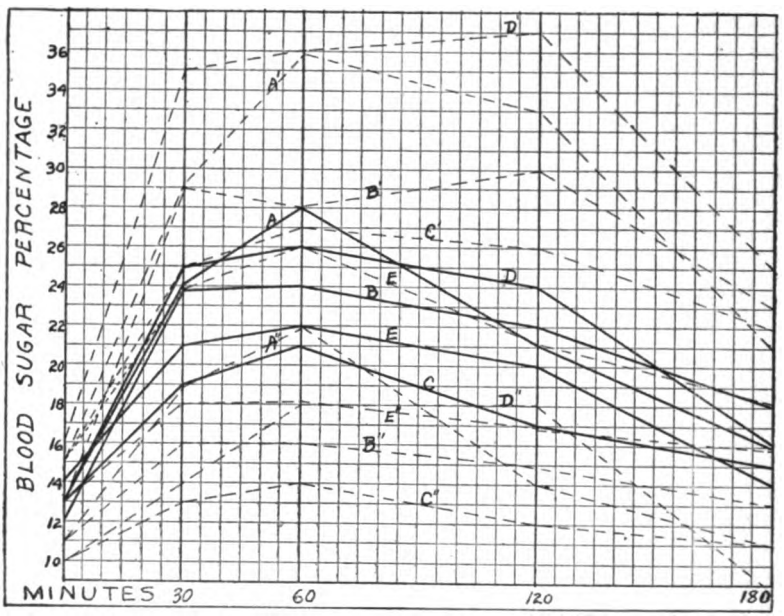

Chart 2.—The heavy black lines represent the average blood sugar curves following the ingestion of 100 gm. of glucose in patients having various basal metabolic rates; the dotted lines represent the upper and lower limits of each group. *A*, *A'* and *A''*, average, upper and lower limits for seven cases with basal metabolic rates between + 40 and + 59 per cent.; *B*, *B'* and *B''*, six cases between + 11 and + 39 per cent.; *C*, *C'* and *C''*, ten cases between — 40 and — 11 per cent.; *D*, *D'* and *D''*, sixteen cases above + 60 per cent.; *E*, *E'* and *E''*, four cases between — 10 and + 10 per cent.

studied by us to be of diagnostic value, in spite of the fact that high and prolonged curves were more frequently found in patients with hyperthyroidism than in those with hypothyroidism.

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CONCLUSIONS

The basal metabolic rate, which is a determination of the heat production in a person under standard conditions, serves as a measurement of the most fundamental process of life itself. Variations of the heat production, and alterations in the body temperature are to be considered rightly a means of fundamental disease classification, and the basal metabolic rate serves as an accurate diagnostic aid in the recognition of the presence or absence of hyperthyroidism.

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DETERMINATION OF THE BASAL METABOLISM

AS A METHOD OF DIAGNOSIS AND AS A GUIDE TO TREATMENT

JAMES H. MEANS, M.D.
BOSTON

The preceding papers in this symposium have set forth the fundamental principles of the subject in hand, human calorimetry and the basal metabolism of man.

It will be my purpose to discuss briefly the rôle that calorimetry plays in the clinic of today, the help that calorimetric observations may be expected to give to the clinician both in diagnosis and in therapeutics, and the nature of this help, particularly its extent and its limitations.

The medical profession of this country is indebted to Atwater and to Benedict and to their collaborators for a vast fund of information on the energy metabolism of the normal human being under nearly every conceivable condition. To Benedict also and his collaborators, and to Du Bois and his collaborators, the profession is indebted for the introduction and application of the science of calorimetry to clinical problems. It was with the development of an accurate surface area formula by Eugene H. and Delafield Du Bois [1] that clinical calorimetry really became a practical possibility, for it supplied the previously lacking prime requisite, an accurate method of judging of the normality or lack of normality of any given person's metabolism.

Since the advent of this formula, the measurement of the gas exchange and the calculation of the heat

1. Du Bois, Delafield, and Du Bois, E. F.: The Measurement of the Surface Area of Man, Arch. Int. Med. 15: 868 (May) 1915.

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production therefrom, that is to say, indirect calorimetry, has come into increasingly wide use in American clinics, so that today there is a reasonably extensive literature on the subject. The work of Boothby [2] at the Brigham Hospital, Boston, and that with which I [3] have been concerned at the Massachusetts General Hospital, is, I believe, among the earliest of the sort. The latter work was begun in 1914.

The practical application of calorimetry to the clinic has been chiefly in the group of thyroid diseases, and in the following remarks it is with them I shall have chiefly to deal. In other fields, however, certain helpful information has been gathered which I shall discuss briefly a little later on.

Before considering the metabolism in disease, a remark is in order regarding that of the normal person. The physiologist is oftentimes impressed with the unaccountable variations in metabolism of essentally similar normal persons, and for that reason he may feel that the clinician is not justified in assuming a definite standard for normal metabolism, as is now done. From the physiologist's point of view, he is correct. There are differences in the metabolism of normal persons that are not explainable on the basis of size, weight, form, age or sex. Nevertheless, these variations are slight compared with the gross differences found in disease. The physiologist, accustomed to measuring bodily processes by methods of precision, is impressed by the slight differences which the metabolism of normal subjects shows; the clinician, on the other hand, obliged as he generally is to estimate abnormalities of function by the qualitative information gained by observation at the bedside, is impressed by the constancy of the metabolism of normal persons.

We are familiar with a number of physiologic constants. None of these are constant in an absolute sense. They are, so to speak, relative constants. From one

2. Boothby, W. M.: Boston M. & S. J. **175**: 564 (Oct. 19) 1916.
3. Means, J. H.: Boston M. & S. J. **174**: 864 (June 15) 1916.

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point of view they may not be constants at all; from another they may present a high grade of constancy. For example, any change in the reaction of the blood except within a minute range is incompatible with life. Indeed, our whole physiologic economy in a sense seems to be regulated to preserve this factor constant. It is one of the most striking constants in nature, and yet within a narrow range it is a variable. The same may be said of the body temperature, the basal metabolism, and in a very limited way of the pulse rate.

It would seem absurd to say that the normal pulse rate is a constant; it is not, and yet it varies within sufficiently understood limits for us to recognize pathologic rates, tachycardia and bradycardia. To that extent it may be considered a constant. It would be equally absurd to fix any arbitrary limits above or below which a pulse rate was considered abnormal; but this does not prevent us from saying that a resting pulse of 40 is a bradycardia or one of 90 a tachycardia. The same reasoning may be applied to the basal metabolism. Only here the normal range of variation is distinctly less than in the case of the pulse. It is more nearly a constant than is the pulse, and is therefore a more accurate index of disturbed function than is the pulse, at least as between different individuals. With the metabolism, as with the pulse, it is illogical in a sense to fix arbitrary limits of variation and to consider the metabolism abnormal if it falls outside them. Yet for convenience we may do so if we at all times bear in mind the arbitrariness of the procedure. When we say that a given patient has a bradycardia, we are in our own minds fixing an arbitrary low limit for the normal pulse. This is a justifiable and useful mental process. It is legitimate to do the same in the case of the metabolism.

In interpreting the significance of abnormal metabolism findings in patients, we must correlate them with clinical findings and weigh their probable importance in

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comparison with every other sort of evidence in any given case, exactly as we should do in interpreting any other laboratory or special finding, such as roentgen-ray, phenolsulphonephthalein test, blood sugar, and the like. We must not rush off and say that, because a given patient's metabolism was 25 per cent. above the normal standard or prediction figure, he has hyperthyroidism. The high finding may have been due to some other disease, pernicious anemia, or leukemia perhaps, or possibly to the fact that although we neglected to take his temperature he had a fever at the time the test was made. Such warnings might seem to be unnecessary, but yet I feel that with the wide popularity that clinical calorimetry has suddenly met, they are in order. So too, is a warning against inaccurate technic in order. This has already been given by various writers. It will bear repetition, particularly for the reason that various instrument makers are exploiting the sale of metabolism apparatus and are trying to convince the practitioner that he needs a metabolism machine in his office quite as much as he does a stethoscope in his pocket. Furthermore, simplified metabolism apparatus of one sort and another is making its appearance in the advertising pages of our journals before it has been described in their scientific columns. The widespread application of calorimetry by persons who do not take the trouble to acquaint themselves thoroughly with the literature and technic of the procedure is fraught with danger, danger to the individual patient through faulty interpretation of results, danger to the profession at large through the publication of erroneous results, that is to say, to the reporting as evidence of a pathologic condition in the patient an abnormal finding which is in actuality the result of technical error.

I am frequently asked either by practitioners or by clinics whether they ought to set up a metabolism laboratory. I tell them that I cannot see that they are under any obligation to do so, and that whether or not

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it will be desirable for them to do so will depend on their special needs. The up-to-date clinic is really obliged now to make Wassermann tests; as I see, it is not at all in that sense obliged to make metabolism determinations. The metabolism determinations in the management of thyroid cases, for it is with them that it has its chief use, is in general a refinement rather than a necessity. We could undoubtedly take reasonably good care of typhoid patients if we were deprived of the clinical thermometer; so we can with our thyroid patients without a metabolism apparatus. The metabolism determination in the thyroid case is of less importance than is the thermometer in typhoid. Furthermore, it is easier to make inaccurate observations with a metabolism apparatus than with a thermometer. It is far better to make no metabolism tests than to make them inaccurately. But, with these warnings and limitations in mind, it seems to me that it can be said that, for the clinic or practitioner handling a considerable number of thyroid cases, facilities for making metabolism observations will be a help. They will give a somewhat more accurate conception of the intensity of the disease than will clinical observation alone; they will add a quantitative aspect to the impression of the case that will, to say the least, be of assistance; and in the differential diagnosis of borderline cases they will be very valuable.

The actual help afforded in thyroid disease can best be observed by some illustrative cases. My purpose at the present time is not in the least to discuss the treatment of hyperthyroidism. The cases that I shall present will be for the purpose of showing what the metabolism determination adds to our impression of a given patient's disease.

It is well recognized that one of the main functions of the thyroid is to regulate the intensity of combustion within the body. When it is overactive, the basal metabolism is increased; when underactive it is decreased, above in the former instance or in the latter

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below what the individual's level would be if he were in a normal state. The order of magnitude of these changes is somewhere in the neighborhood of a drop of from 20 to 40 per cent. in myxedema, and an elevation of from 20 to 40 per cent. in mild, 40 to 60 per cent. in moderate, and 60 to 100 per cent. in severe hyperthyroidism. The determination of the metabolism in the thyroid cases constitutes essentially a functional test of that gland.[4]

The progress of a febrile disease is rendered more easy of visualization by the clinical chart. The clinical chart in pneumonia or typhoid consists of pulse, temperature and respiration curves—these are the three factors of cardinal importance. A clinical chart in thyroid disease also helps visualization of progress. But here the factors of first importance are the basal metabolism, the pulse and the body weight. These three curves, when plotted, give us information of a similar nature to that given by the usual chart of the febrile patient.

It is the construction of such charts that has interested us most at the Massachusetts General Hospital.[5] A series of observations, when extended over a period of months or years, gives a very striking picture of the patient's progress. Such series, I believe, in general are of considerably more importance than isolated observations.

Let us consider a few of these by way of illustration. In the typhoid patient's chart the perpendicular lines represent days. The diseases of the thyroid are for the most part chronic. In our thyroid chart, therefore, the perpendicular lines are months; and while the typhoid chart at most covers a matter of a few weeks, the thyroid chart may well be extended for a period of years.

4. Means, J. H., and Aub, J. C.: A Study of Exophthalmic Goiter from the Point of View of the Basal Metabolism, J. A. M. A. **69**: 33 (July 7) 1917; Basal Metabolism in Exophthalmic Goiter, Arch. Int. Med. **24**: 645 (Dec.) 1919; Basal Metabolism in Hypothyroidism, ibid. **24**: 404 (Oct.) 1919.

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ILLUSTRATIVE CASES

CASE 1.—Chart 1 is that of a man with severe exophthalmic goiter of fourteen months' duration untreated and progressing unfavorably at the time, Nov. 18, 1919, he first came to our clinic. The disease had begun while he was in the army. The chart shows at a glance the progress of this patient for a period of a year and the treatment that he received. Three operations were done by Dr. E. P. Richardson: November 24, ligation of the right superior vessels; December 1, of the left,

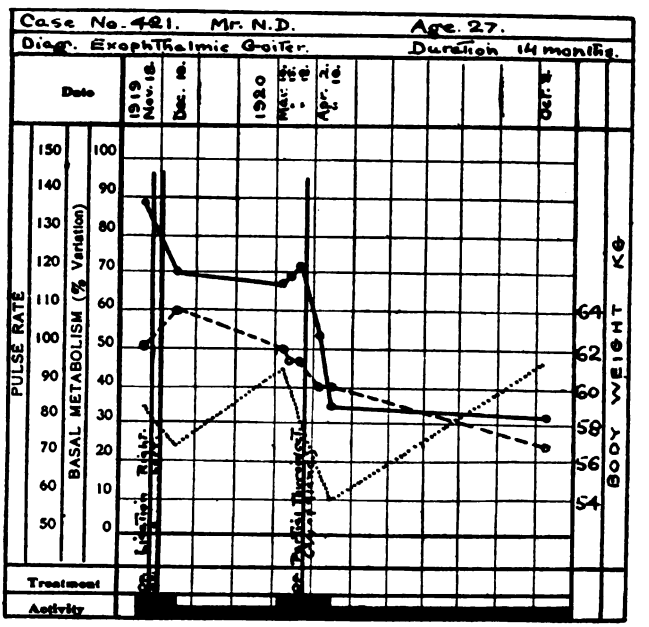

Chart 1 (Case 1).—Basal metabolism (per cent. of variation from Sage Institute standard) shown by the solid black line and dots; pulse, by interrupted line and circles; weight, by the dotted line. Under "Treatment," the type and time of operation is shown. Under "Activity," the rest factor is indicated. When the space is entirely black it denotes complete rest in bed; half black, partial rest; when blank, that the patient is following his ordinary mode of life. The same system will be followed in the succeeding charts.

and, March 24, 1920, a subtotal thyroidectomy. About three quarters of the gland was removed. After the ligation there was a slight fall in metabolism and pulse and a slight gain in weight; after the thyroidectomy, a striking fall in metabolism, all of which occurred in the fortnight after operation. Six months after operation the metabolism was essentially unchanged, still being plus 32 per cent. The patient had

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gained weight and his pulse had fallen to a normal level. Clinically he was much better, but still had some nervousness, tremor and increased sweating. He was not yet able to do a full day's work.

CASE 2.—Chart 2 is that of a schoolmistress of 38 with a rather mild form of exophthalmic goiter which she had had apparently for only two months at the time she first visited the clinic. The chart shows her progress over a period of twenty-one months, during which time she received seven roentgen-ray treatments from Dr. George W. Holmes with absolutely nothing else in the way of therapy. She pursued her normal mode of life and continued with her teaching. Oct. 2, 1920, she was subjectively and objectively well, as, indeed,

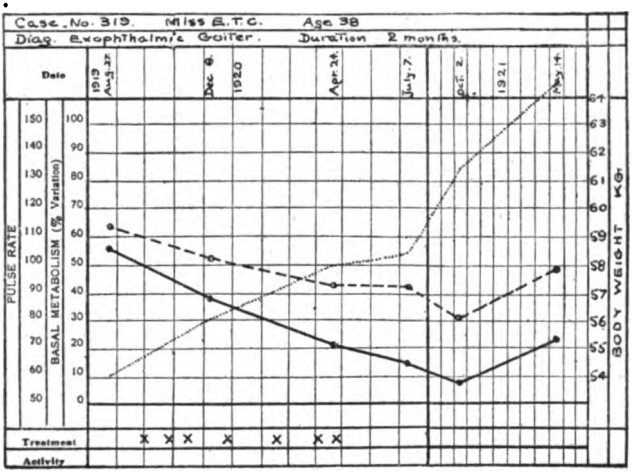

Chart 2 (Case 2).—Under "Treatment," X denotes a roentgen-ray treatment. It will mean the same in succeeding charts.

she also was on May 14, 1921, though at that time metabolism and pulse showed a slight upward trend. This rise may or may not be of importance. But it illustrates, it seems to me, the usefulness of the chart, for it puts us on our guard against a possible relapse which we might have missed on the basis of the clinical picture alone.

CASE 3.—Chart 3 is that of a girl of 21 with the characteristic symptoms of hyperthyroidism but with only a very slight fulness of the thyroid and with no eye signs. The picture was what one may call, for want of a better name, simple hyperthyroidism. Her chart covers a period of about a year. During that time she had been taking quinin hydrobromid, 5 grains, three times a day, and for about half the time ergotin, 1 grain, three times a day. As shown in the chart also, she

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had had partial or complete rest for a year. Roentgen-ray treatment was started, May 18, 1920. August 11, she had had five treatments, with a marked fall in metabolism and pulse and a gain in weight, and definite subjective and objective improvement. In the fall of 1920 she had a relapse with return to about the starting point. A second course of roentgen-ray treatment seems to be relieving this, much as it did in the first instance.

Case 4.—Chart 4 is that of a man, aged 27, with severe exophthalmic goiter of a year's duration, who had been having complete rest and quinin hydrobromid for three months

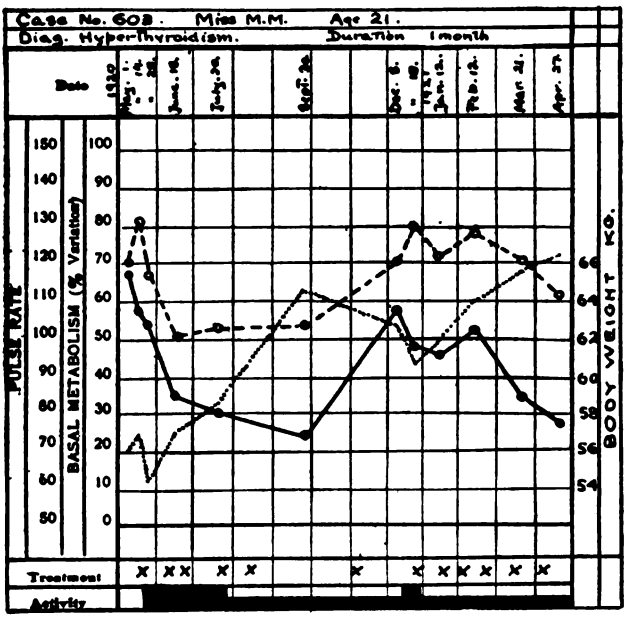

Chart 3.—Basal metabolism, pulse and weight in Case 3.

under the direction of Dr. Charles A. McDonald when he was referred to the clinic. His symptoms had begun the year before while he was serving in the navy. This patient received essentially no treatment but roentgen ray. Between March 25 and July 7, 1920, he received six full treatments. During this period he was not working but was reasonably active and had no real rest. There was a most astounding fall in basal metabolism and pulse, and gain in weight. There was a corresponding clinical improvement; this was so great that against advice he returned to work. His work, that of chauffeur on a fire truck, was hardly of a suitable sort for a man

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recently ill with exophthalmic goiter. The not surprising result was that he again became thyrotoxic, which is well shown in the chart. In spite of this he has continued at work and, even under these adverse circumstances, a second course of roentgen-ray treatment seems to be curing him.

CASE 5.—Chart 5 shows the findings in the case of a woman, aged 31, who had had moderately severe exophthalmic goiter for about a year at the time the chart was started. Eleven roentgen-ray treatments (seven before the chart was started) had failed to accomplish any clinical improvement or to

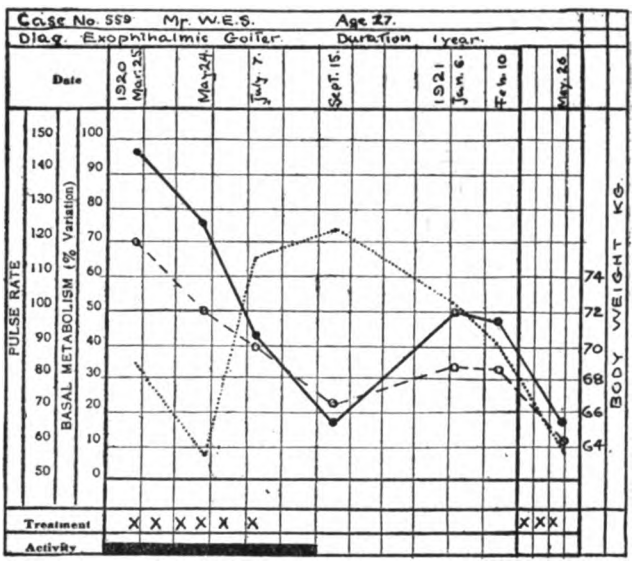

Chart 4.—Basal metabolism, pulse and weight in Case 4.

reduce her metabolism below plus 65 per cent. It might be said, however, that she had followed her ordinary mode of life during this period. A short rest in bed in the hospital then reduced her metabolism some 15 points and, March 26, 1920, Dr. C. A Porter ligated the superior arteries on each side. Two months later the metabolism had remained at the lowered level, but had shown no further drop. Dr. Porter operated again and, June 16, 1920, did a subtotal thyroidectomy. There was a prompt clinical improvement after that and fall in pulse and metabolism. Eleven months after the last operation the metabolism was plus 24 per cent.; the patient had gained considerable weight and clinically was practically well.

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Case 6.—Chart 6 illustrates the effect of overirradiation in exophthalmic goiter. This patient, a woman aged 29, had a rather mild form of the disease which she had had for a year. Four roentgen-ray treatments were given between Jan. 16 and March 22, 1920, and from January 12 to February 11 she had complete rest in bed in the ward. She showed a marked clinical improvement and fall in metabolism and pulse. The treatment was stopped. April 28, 1920, she reported for observation. Within the last three weeks she had gained a great deal of weight; her face had become puffy and she complained of feeling dull and dopey. The picture was essentially that of myxedema. The metabolism was minus 11 per cent. She was started on thyroid gland, 1½ grains per day. May

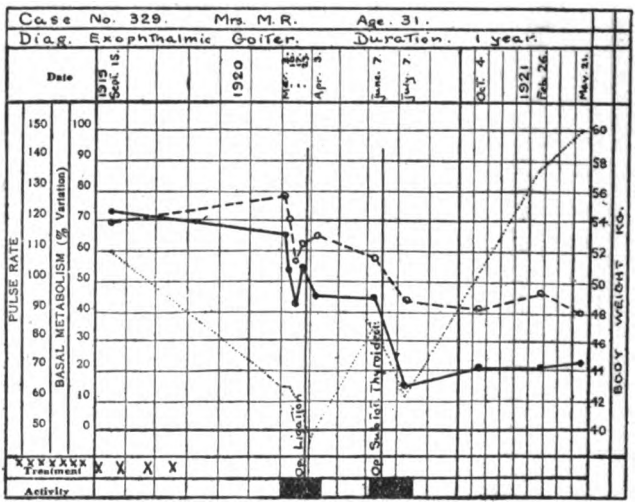

Chart 5.—Basal metabolism, pulse and weight in Case 5.

14, her metabolism had returned to normal. The thyroid was stopped. May 20, the metabolism had fallen again to minus 11 per cent. Thyroid administration was begun again, but in a smaller dose, 1½ grains every other day. July 28, her metabolism was plus 10 per cent., and all symptoms of hypothyroidism had gone. The thyroid was stopped. She was followed for nine months more. The metabolism never fell again, and no symptoms of myxedema returned; indeed, on the last observation, May 5, 1921, the metabolism was slightly supernormal, indicating that perhaps a return of her hyperthyroidism was impending, though clinical signs were lacking. This case shows from both the clinical and laboratory points of view that, in certain cases at least, irradiation really seems to lower thyroid activity. It also shows that in the

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roentgen-ray treatment of exophthalmic goiter the possibility of overtreatment must be borne in mind and guarded against. The very delicate response of the metabolism level to thyroid administration is also well shown by this chart.

CASE 7.—Charts 7 and 8 are of patients with hypothyroidism. Figure 7 is that of a woman, aged 35, with frank myxedema which had existed for four years. The metabolism was promptly returned to normal by thyroid administration. At the same time the weight fell and the symptoms improved. The effect of a reduction in thyroid dosage is shown in the chart, a fall in metabolism and pulse. The dose was again increased, with a return of the metabolism toward normal.

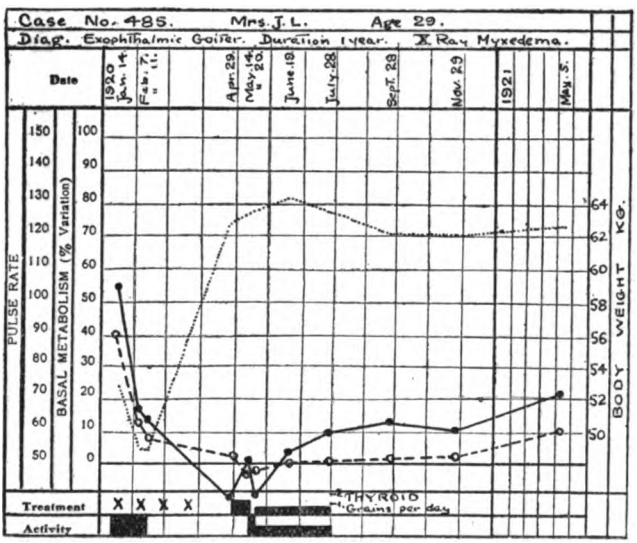

Chart 6 (Case 6).—Under "Treatment," the thyroid dosage is indicated by shading. The first dose employed was 1½ grains per day; the next, 1½ grains every other day.

This patient has been followed for well over a year. In the main her metabolism has been within normal limits, and she has been free from symptoms. At the time of her last visit, because of a slight tendency to subnormal metabolism and steady gain in weight, she was told to increase the dose of thyroid still further.

CASE 8.—Chart 8 also illustrates the control of thyroid dosage by metabolism findings. This patient, a man, aged 29, did not have frank myxedema; he had suggestive signs only: a tendency to gain weight, and some sluggishness, both mental and physical. He was found to have a subnormal metabolism and was started on thyroid; 4½ grains a day

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brought his metabolism to normal, then a decrease to half that dose was followed by a fall. The original dose was resumed and now for a year and a quarter his metabolism has been kept essentially within normal limits, and clinically he has been much improved.

COMMENT

These eight charts, it is hoped, will illustrate what to my mind is the chief rôle of indirect calorimetry in the clinic of today; namely, the quantitative estimation of

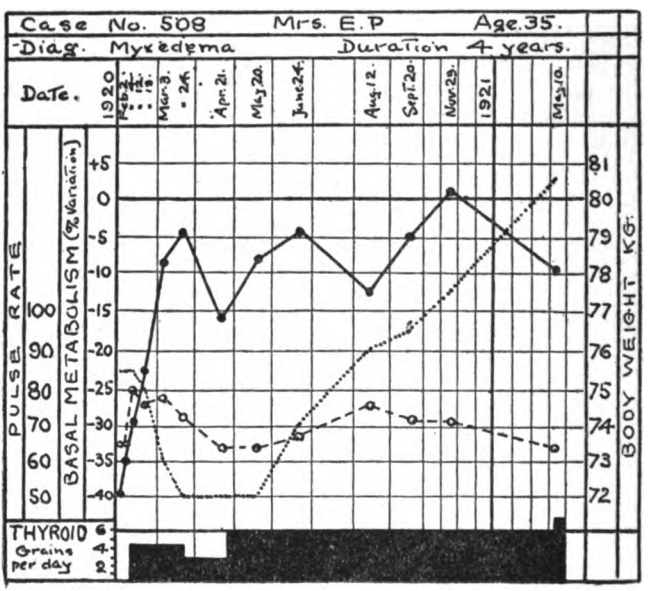

Chart 7 (Case 7).—In this and in Figure 8, "Activity" is not indicated. Both these patients pursued throughout a normal life. The dose of thyroid employed is indicated by the width of the black area.

thyroid function and the accurate representation of the effects of treatment, either those measures in hyperthyroid states which are designed to reduce thyroid activity, or thyroid therapy in conditions of hypothyroidism. In the latter, particularly, the discovery of the exact dose of thyroid gland which will make a given patient's metabolism assume and stay at a normal level is most fascinating.

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Outside of thyroid disease, the metabolism determination as a diagnostic procedure or functional test does not play an important rôle. By that I do not mean to say that the study of a variety of pathologic states by calorimetric methods is not of fundamental importance. It most assuredly is; but such studies belong primarily to research, while the matter under consideration is the, so to speak, routine use of calorimetry in the clinic. The place of calorimetry in the investigation of disease does not come within the scope of the present paper.

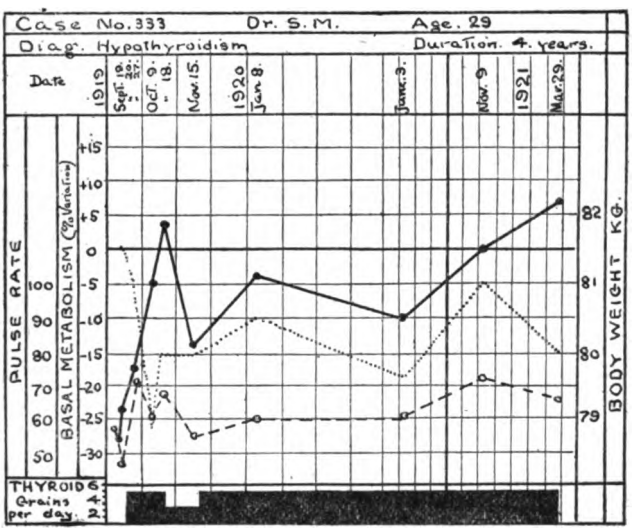

Chart 8.—Basal metabolism, pulse and weight in Case 8.

Before closing, I wish to add merely a few words as to the metabolism determination in the field of differential diagnosis. From what has already been said here and elsewhere, it is obvious that when hypothyroidism or hyperthyroidism is suspected, metabolic studies will be of great assistance in the differentiation of effort syndrome and mild hyperthyroidism, for example, and of toxic from nontoxic goiters, or in the borderline hypothyroid conditions. In my hands it has been par-

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ticularly useful in the recognition of the latter. Chart 8 is an excellent illustration of this.

One other direct clinical application is in the matter of obesity. Studies published elsewhere [6] have shown that in simple obesity the basal metabolism is normal. Such obesity is due, to my mind, to a disproportion between food intake and bodily activity, and not to any fundamental change in the rate of combustion in the body. In such persons the giving of thyroid raises the metabolism to an abnormal level, produces hyperthyroidism, in other words. The treatment, then, of simple obesity with thyroid is in my opinion pernicious. It relieves one evil by creating another. I have, too, been impressed of late with the very common use of thyroid by the laity for purposes of weight reduction. Personally, I think the sale of this drug except on prescription should be prohibited by law. Metabolism studies have convinced me that thyroid should never be given except to persons who exhibit subnormal metabolism.

By means of the metabolism determination, the case of simple obesity can be differentiated from the obesity due to endocrine disease. This applies not only to hypothyroid obesity but to pituitary as well. In hypopituitarism there is a reduction in metabolism level just as in hypothyroidism, though perhaps of lesser degree, so that calorimetry may help us in recognizing obesity of pituitary origin also.

Of diseases other than of the thyroid and pituitary in which there are alterations in basal metabolism, the most striking are the leukemias and severe anemias, particularly pernicious anemia. The significance of these changes, however, is as yet not clearly understood, and they have at present no routine diagnostic or therapeutic bearing, although it is altogether likely that later they may have.

6. Means, J. H.: J. M. Res. **32**: 121, 1915; The Basal Metabolism in Obesity, Arch. Int. Med. **17**: 704 (May) 1916. Means, J. H., and Woodwell, M. N.: Ibid. **27**: 608 (May) 1921.

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In conclusion, I will simply reiterate that indirect calorimetry has furnished us with a quantitative test of the thyroid, with a method for clearly visualizing the progress of patients with thyroid disease, of accurately controlling the treatment of them, and of clinching the diagnosis in certain borderline cases. It also has thrown light on the nature of obesity and has furnished us with a means of distinguishing between simple and endocrine obesity, and has demonstrated the inadvisability of treating the former condition by the administration of thyroid gland.

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THE BASAL METABOLISM IN FEVER*

EUGENE F. DU BOIS, M.D.
NEW YORK

The clinician has several definite and practical questions to ask regarding the basal metabolism in fever. He wishes to know whether he can calculate the total metabolism of a patient with a given degree of temperature in order to have a rational basis for the fever dietary. It is important for him to know whether there is anything abnormal in the metabolism of proteins, fats, carbohydrates and water. Being interested in the whole subject of fever, he desires information regarding the relative importance of the various factors which increase the metabolism in hyperthermia.

The answers to the questions must be sought in the voluminous literature of the last thirty years. We have at our disposal a large number of experiments on animals with fever produced by lesions of the central nervous system, by drugs and by artificial infections. These have been well reviewed by Richter,[1] and more recently by Barbour,[2] but they do not give us much help in our problems with man. We have a few experiments on men warmed artificially by hot baths, but in these the effect of the external heat outweighs the fever. We have a large number of experiments on fever patients made by the Zuntz-Geppert apparatus, Benedict apparatus and similar machines which measure the heat production by means of the method of indirect calorimetry. These have given us much information and have laid the foundation of our present knowledge of the metabolism in fever. They have certain disadvantages since the subjects are exposed to

* From the Russell Sage Institute of Pathology in affiliation with the Second Medical Division of Bellevue Hospital and from the Department of Medicine of Cornell University Medical College.

1. Richter, P. F.: Fieber, in Oppenheimer's Handbuch der Biochemie.

2. Barbour, H. S.: The Heat-Regulating Mechanism of the Body, Physiol. Rev. 1: 295, 1921.

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different environmental conditions and are more or less disturbed by the application of mouth pieces or masks.

The discussion in this paper will be limited almost entirely to the groups of fever patients studied in the respiration calorimeter of the Russell Sage Institute of Pathology in Bellevue Hospital, New York, between the years of 1913 and 1920. Patients and normal controls have been exposed to uniform conditions of environmental temperature and humidity. They have lain almost motionless on a comfortable bed in a quiet respiration chamber for periods of from two to four hours, and in some instances all night. The temperature has been read every four minutes by means of an electrical thermometer which lies about 10 cm. in the rectum. The heat production has been measured by the chemical methods of indirect calorimetry and by the physical methods of direct calorimetry which determine the exact heat loss by radiation and conduction and by the vaporization of water. Incidentally, we may note that the close agreement of these two methods proves that the law of the conservation of energy holds good in fever patients.

The published work consists of studies in typhoid fever by Coleman and Du Bois,[3] in malaria by Barr and Du Bois,[4] and in tuberculosis by McCann and Barr.[5] The unpublished work here presented consists of studies made by Coleman, Cecil, Barr and Du Bois in erysipelas,[6] arthritis [7] and the fever produced by intravenous injections of protein.[8]

3. Coleman, Warren, and Du Bois, E. F.: Clinical Calorimetry, Seventh Paper, Calorimetric Observations on the Metabolism of Typhoid Patients With and Without Food, Arch. Int. Med. 15: 887 (May) 1915.

4. Barr, D. P., and Du Bois, E. F.: Clinical Calorimetry, Twenty-Eighth Paper, The Metabolism in Malarial Fever, Arch. Int. Med. 21: 627 (May) 1918.

5. McCann, W. S., and Barr, D. P.: Clinical Calorimetry, Twenty-Ninth Paper, The Metabolism in Tuberculosis, Arch. Int. Med. 26: 663 (Dec.) 1920.

6. Coleman, Warren; Barr, D. P., and Du Bois, E. F.: Clinical Calorimetry, Thirty-Second Paper, The Metabolism in Facial Erysipelas, to be published.

7. Barr, D. P.; Cecil, R. L., and Du Bois, E. F.: Clinical Calorimetry, Thirtieth Paper, Observations on the Metabolism in Arthritis, to be published.

8. Cecil, R. L.; Barr, D. P., and Du Bois, E. F.: Clinical Calorimetry, Thirty-First Paper, The Effect of the Injection of Foreign Protein on Metabolism, to be published.

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Comparisons with the normal were made according to the usual method of the Sage investigators, who consider that the normal metabolism for a given age and sex is proportional to the surface area.[9] Practically all of the subjects studied were between 20 and 40 years old, and the standard used for this age was 39.5 calories per square meter per hour.[10] If we express the matter graphically on a chart (Chart 1),

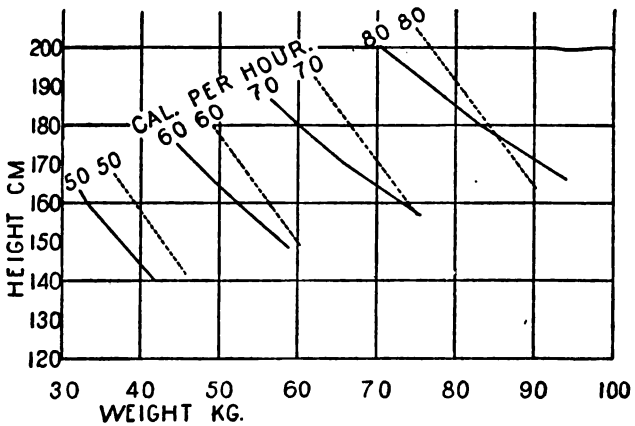

Chart 1.—A comparison of the normal standards for men 30 years old. The solid curved lines give the calories per hour according to the surface area chart and standards of Aub and Du Bois. The dotted lines represent the figures according to the Harris-Benedict multiple prediction tables. For instance, a man 30 years old, 180 cm. tall and 60 kg. in weight would have a predicted normal basal metabolism of 70 calories per hour according to the surface area curves, and about 67 calories per hour by the other method. The results according to the Harris-Benedict formula are lower, but the two sets of lines are almost parallel for this age group.

we can show the curves for the predicted metabolism of normal individuals of different heights and weights. If metabolism were proportional to height, these lines would be horizontal; if proportional to weight, they

9. Du Bois, Delafield, and Du Bois, E. F.: Clinical Calorimetry, Tenth Paper, A Formula to Estimate the Approximate Surface Area if Height and Weight be Known, Arch. Int. Med. **17**: 863 (June) 1916.

10. Aub, J. C., and Du Bois, E. F.: Clinical Calorimetry, Nineteenth Paper, The Basal Metabolism of Old Men, Arch. Int. Med. **19**: 823 (May) 1917.

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would be vertical. If proportional to surface area, they would have the slant shown in the curved solid lines of the chart, and our results do agree with these curved lines. A purely statistical study of the normal basal metabolism by Harris and Benedict [11] has resulted in a height-weight-age formula. With a little calculation we can show their results for men 30 years old on this chart. It is significant that the dotted lines for the Harris-Benedict formula are parallel to the surface area curves.

The studies of large groups of normal controls show that about 90 per cent. of normal men come within 10 per cent. of this standard; but a few who are apparently normal may show figures as much as 15 per cent. above or below.

Can we predict the metabolism as closely as this for any specified degree of fever?

Chart 2 shows the results in all the fevers studied in the calorimeter, expressed by the method used by McCann and Barr in tuberculosis. The ordinates show the rectal temperature in degrees Centigrade. The abscissas show the level of the metabolism in percentage of the average normal. The line 90 means 10 per cent. below the average; 150 means 50 per cent. above the average. Each dot denotes an experiment of from one to three hours at a given temperature level. The normal temperatures were obtained in afebrile periods or in the first eight days of convalescence. The diagonals are sketched to represent the direction of the swarms of dots. It will be seen that in tuberculosis the diagonal crosses the 40 C. line at a level of about 32 per cent. above the normal. In many of these patients there was enough undernutrition to account for a certain diminution in metabolism. In erysipelas the metabolism is a little higher for the same temperature. In typhoid fever, the line crosses

11. Harris, J. A., and Benedict, F. G.: A Biometric Study of Basal Metabolism in Man, Publication 279, Carnegie Institution of Washington, 1919.

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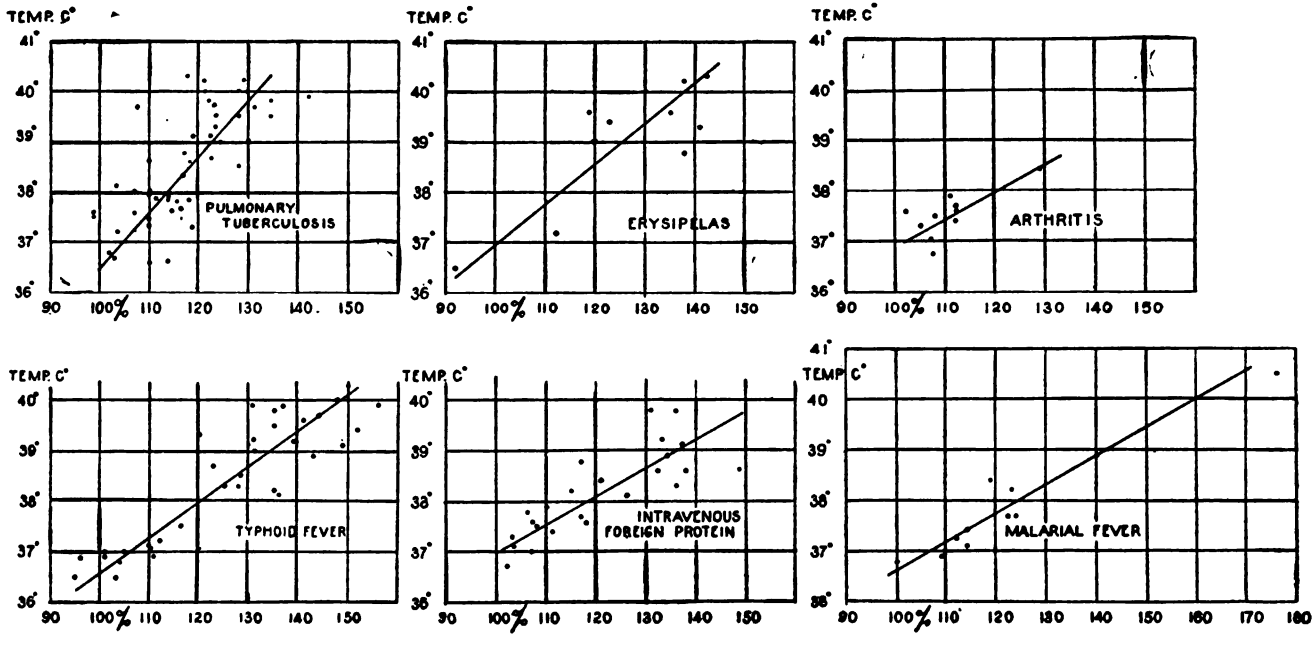

Chart 2.—Relationship of basal metabolism to temperature in various fevers. Ordinates represent rectal temperance in degrees centigrade, abscissas the metabolism expressed in percentages of the average normal; e. g., 150 equals 50 per cent. above the average. Each dot represents a calorimeter experiment of from one to three hours at the given temperature.

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the 40-degree level at 48 per cent. above the normal metabolism. In malaria and the fever following the intravenous injection of foreign protein, the metabolism is slightly higher. Of course, it is necessary to leave out the shivering periods in these two conditions. It is possible that some of the results in the high temperature following the chill are slightly affected by the previous severe muscular exercise.

Most of the patients whose metabolism is very high for the degree of temperature were typhoid or malaria patients with a high level of protein metabolism. Most of those with low basal metabolism were tuberculous patients with low protein metabolism. We know that protein increases the metabolism through its specific dynamic action, and this may explain the difference between the groups of patients. The ingestion of a large protein meal does not increase the heat production in typhoid fever, in which the protein metabolism is already high, but it does cause a striking increase in tuberculosis, in which the protein metabolism is at a much lower level. Although the increased protein metabolism seems to be a factor of some importance, we believe that it is outweighed by another and simpler factor.

We note particularly the similarity between fevers of greatly different origins, such as typhoid and erysipelas, malaria and intravenous injections. We are impressed by the importance of the nonspecific element in fevers. This is even more striking, if we group all the heterogeneous fevers in one chart (Chart 3). The continued diagonal line is here drawn from statistical calculations, and the dotted lines are placed to represent divergences of 10 per cent. from this average. Out of the total of 137 experiments in various fevers, 82 per cent. come within 10 per cent. of the average. In other words, the percentage variations in the metabolism for a given temperature are scarcely greater than in a similar group of normal individuals.

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This surprising uniformity of results suggests at once that we are dealing with the law of physical chemistry enunciated by van't Hoff.[12] For ordinary temperatures the van't Hoff law can be thus expressed: "With a rise in temperature of 10 degrees Centigrade, the velocity of chemical reactions increases between two and three times." In other words, the temperature coefficient is usually between 2 and 3. This means an increase of from 30 to 60 per cent. for the 3 degree rise from 37 to 40 C. Practically all of the fever experiments are within these limits, and the average line shows a temperature coefficient of 2.3.

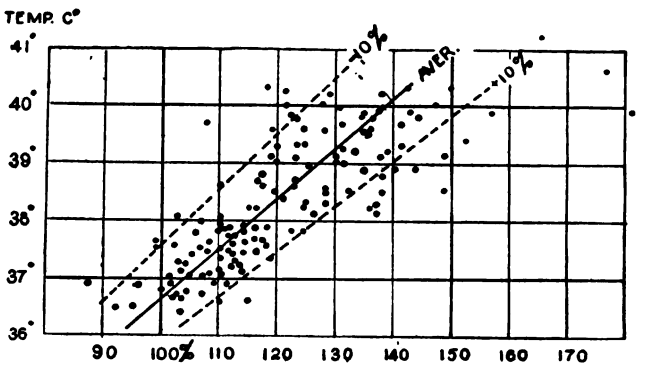

Chart 3.—Results in six different fevers grouped in one chart. The continued line shows the average and the dotted lines are drawn to represent metabolism 10 per cent. above and 10 per cent. below the average.

Van't Hoff and Kanitz[13] give the temperature coefficients which show the rate of increase in a number of chemical reactions with an equal rise in temperature. If we plot these in exactly the style of the fever patients (Chart 4) we note that the lines have approximately the same slope. In other words, the reactions in a fever patient respond to a rise in tem-

12. Van't Hoff, J. H.: Studies in Chemical Dynamics, Revised by E. Cohen, Translated by T. Ewan, Easton, Pa., Chemical Publishing Company, 1896.

13. Kanitz, A.: Temperatur und Lebensvorgänge in Biochemie in Einzeldarstellungen, Vol. 1, Berlin, Gebrüder Borntraeger, 1915.

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perature in a manner which resembles closely the chemical reactions in a test tube suspended in a water bath.

There is a tremendous gap between the simple reactions in the test tube and the complex oxidations in the diseased human body, and we should hesitate to compare them were it not for the large number of biologic reactions which show temperature coefficients between 2 and 3. Van't Hoff calls attention to the rate of carbon dioxid elimination in plants, which shows a coefficient of 2.5. Kanitz [18] gives a long list of similar coefficients for plant respiration, rate of isolated hearts, contraction of smooth muscle and the metabolism in cold blooded animals.

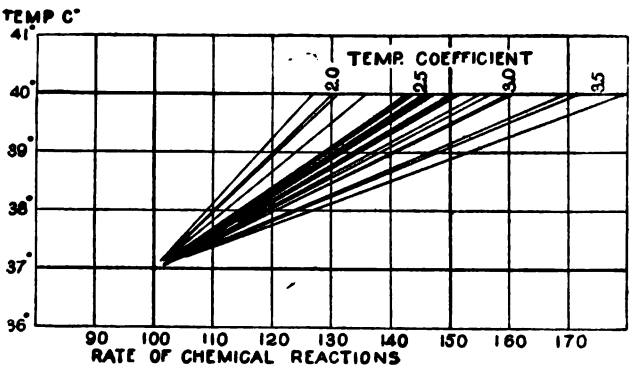

Chart 4.—The lines in this chart represent a number of typical chemical reactions taken from van't Hoff and Kanitz. The slant of the lines shows the increase in the rate of the reactions as the temperature is raised. Note that the lines correspond closely to those which represent the total oxidations in the human body.

We have seen that the gross results in different fevers are strikingly similar. It is interesting to note the similarity in the details of the mechanism of the rise and fall of temperature in the chills of malaria and those which follow the intravenous injection of foreign protein. The first curve (Chart 5) shows the results obtained in a malaria patient by Dr. David P. Barr and myself. Before the chill the metabolism and temperature were normal. In the period of the thirty-four

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minute chill there was terrific shivering, and as a result the heat production rose to 216 per cent. above normal. After the chill the metabolism was increased by the hyperthermia, and then fell gradually as the temperature became lower. The chill was accompanied by no change in the heat elimination. The old idea that the rise in temperature is largely caused by a decreased

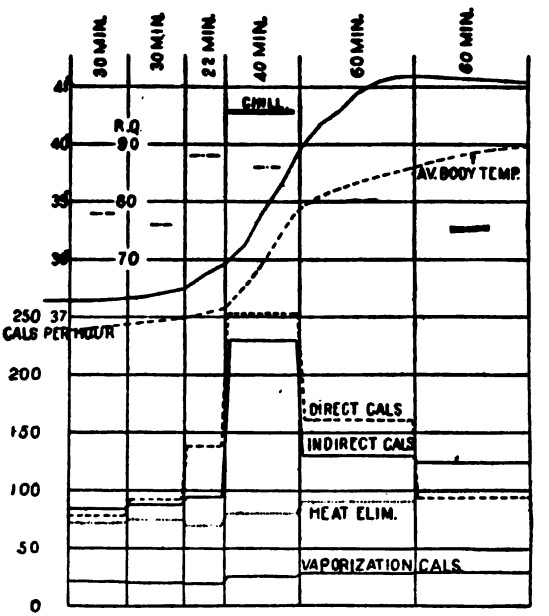

Chart 5.—Calorimeter results during a malarial paroxysm. The upper continued curve shows the rectal temperature.

elimination has been proved false. The rise is due to the increased heat production, and this is caused in part by shivering and in part by some chemical regulation the nature of which is still in doubt.

After the temperature has reached its zenith, the elimination must, of course, exceed the heat production.

The curve of the rectal temperature does not always parallel the curve for the changes in the average body

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temperature. We shall never know the exact level of the average body temperature, because we cannot place thermometers all over the extremities and in the viscera; but if we know the differences between heat production and heat elimination, we can calculate how many calories have been stored in or lost from the body, using the method devised by Barr.[4] If we start the average temperature curve half a degree below that of the rectal temperature, we can then follow

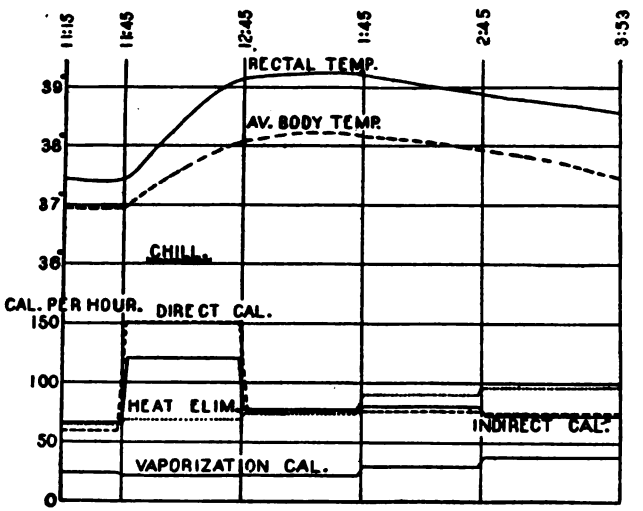

Chart 6.—Calorimeter results following the intravenous injection of 35 million dead typhoid bacilli. The percentage rise in metabolism does not appear so great because the chill occupied only a portion of the period between 11: 45 and 12: 45.

its changes. Apparently the region whose temperature is measured by a thermometer deep in the rectum shows a more rapid rise than the whole body, with its large mass of tissue near the surface and in the extremities.

The curve of the arthritic patient who was given an intravenous dose of 35 million dead typhoid bacilli is almost identical with that of the malaria patient (Chart 6).

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A study of the respiratory quotients in various fevers indicates that there are no significant changes in the metabolism of fat and carbohydrate. Protein metabolism is high in fevers, and the protein minimum or "wear and tear quota" cannot be reduced to the normal level. This increase seems to be proportional to the toxemia, since it is excessive in patients seriously ill with typhoid and erysipelas, and comparatively insignificant in chronic tuberculous patients with the same degree of fever.

Balcar, Sansum and Woodyatt have produced excessive fever in dogs by depleting the water reserves of the body, and they infer [14] that an abnormal water metabolism may be the cause of fever in man. If this were the case, we should expect to find striking abnormalities in the total or percentage loss of heat through vaporization in febrile patients. A careful scrutiny of the calorimeter results shows no such phenomenon. The water metabolism of fever patients corresponds closely with that of patients with an equal percentage rise in metabolism caused by hyperthyroidism.

Let us now answer the original questions. We can say that it is possible to estimate the basal metabolism of a patient by calculating his normal according to surface area standards. To this we should add about 13 per cent. for each degree Centigrade above the normal temperature (7.2 per cent. for each degree Fahrenheit). This should be increased by 10 per cent. in the case of toxic patients with great destruction of body protein, and by approximately 10 per cent. in all other febrile patients who are receiving much food. A further allowance of from 10 to 30 per cent. for muscular activity may be necessary if the patients are restless.

It is interesting to note that our practical calculations in the clinic are based on the law of the conservation of energy, on the surface area law of Rubner, on the laws

14. Balcar, J. O.; Sansum, W. D., and Woodyatt, R. T.: Fever and the Water Reserve of the Body, Arch. Int. Med. 24: 116 (July) 1919.

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of the specific dynamic action of foods as formulated by Rubner and Lusk,[15] and on the temperature law of van't Hoff.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. PLUMMER, BENEDICT, LUSK, BOOTHBY, MEANS AND DU BOIS

DR. GEORGE W. CRILE, Cleveland: I wish to assent to the statement by Dr. Boothby that the roentgen ray does not control exophthalmic goiter. We have often seen great benefit following roentgen-ray treatment, with recrudescence as a rule. At present we have no accurate and absolute basis for the classification of exophthalmic goiter. I do not think that the classification may be based safely on the histologic study of the thyroid. Usually it is impossible to make the classification by the variation in the basal metabolism rates. I operate on quite a few patients who do not show alteration in the basal metabolic rate, and yet we secure good clinical results. I think that the most important points are taking a careful history and making a careful physical examination. After that the basal metabolism rate is of great importance, but I would not regard it as being of pathognomonic importance, nor would I classify exophthalmic goiter wholly on basal metabolism rates. I was glad to hear Dr. Boothby say that he does not think basal metabolism measurement would be a true guide for projecting a surgical operation. We feel that the best guide, after all, is the judgment of the surgeon or physician. For example, the basal metabolism rate will tell you what rate of expenditure the body is making; but it does not tell you how much reserve there is in the myocardium, in the liver and in the central nervous system. If surgery will avail itself of all its opportunities of minimizing to the utmost degree the impression made on the patient, every patient will be operable.

DR. CHARLES H. MAYO, Rochester, Minn.: After all, the importance of the subject relates mostly to chronic diseases and especially to diseases of the thyroid, in the changes of basal metabolism incident to normal, hypothyroid or hyperthyroid function. Enough is now known concerning the thyroid, its function and diseases so that in severe types of hyperthyroidism, basal metabolism determination, while not the sole indicator of severity, is of importance considered with the symptoms. Without it psychoneurosis, in which the Goetsch or epinephrin test shows a low stability of the nervous system, altogether too variable a test for much dependence in the analysis of exophthalmic goiter, might be classified in the category of hyperthyroidism.

15. Lusk, Graham: Science of Nutrition, Philadelphia, W. B. Saunders Company, 1919.

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DR. JOSEPH AUB, Boston: We are just completing some work in our laboratory to see whether the tremor of hyperthyroidism or the tonus of the muscles could be the cause of the increased metabolic rate. The work was done on cats. Their normal metabolism was first determined. Thyroxin was then injected intravenously and intramuscularly and the effect watched by following the metabolic rate. When well intoxicated, the animals were anesthetized with urethane, and their metabolism further studied. Its level remained approximately the same, in spite of the fact that the tremor of the muscles was absent and the muscles felt flabby. If later we cut all the nerves to the limbs, and so eliminated all tonus of these muscles, the metabolism did not return to its normal level. Therefore, the conclusion is suggested that muscular activity and tonus are not the main features in the high metabolism of hyperthyroidism, and this work supports the view that the body cells themselves increase their usual basal rate of oxidation.

DR. FRITZ TALBOT, Boston: It seems to me that true basal metabolism cannot be obtained in children under 10 years of age with the mouth and nose piece, but must be obtained in the respiratory chamber. It surely cannot be obtained in children 6 years of age. Consequently, I would give warning to draw no interpretations from findings obtained with apparatus using the nose and mouth piece, except in those children who have been thoroughly trained to the apparatus, so that there is no element of excitement, and those who can keep absolutely quiet. The second point I would like to make is that the interpretation of results in childhood is fraught with more dangers than in the adult. The reason is that childhood and infancy is the period of rapid change. The standards to be used change accordingly and looking at the chart of the metabolism per unit of body surface you will see that there is a very marked change in metabolism during the first year and a half or two years of life. Another point: Malnutrition in infancy is quite different from malnutrition in the adult. Two or three speakers have said that in malnutrition you expect a lowered basal metabolism. The reverse is the truth in severe infantile malnutrition (infantile atrophy). The basal metabolism is above the average, sometimes 60 or more per cent. Then, in regard to the subject that receives most attention, hypothyroidism and hyperthyroidism: I have recently been able to study two infants, 3 months of age, who clinically were early cretins; one of them had a basal metabolism of minus 18 per cent., and the other had a normal basal metabolism. One was in the state of hypothyroidism and the other was not. Finally, it is generally assumed that at puberty there is no increase in the basal metabolism. Two or three of Benedict's and my cases show an increase in the metabolism, and I have recently been studying selected girls from our outpatient department who

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at puberty have palpable thyroids. The tendency of this selected group is to show a definitely increased metabolism.

Dr. Graham Lusk, New York: I would ask Dr. Boothby to withdraw the definition, "specific dynamic action" of thyroxin. If the term came to be applied to such diseased conditions as manifest an increased heat production, the disturbances would then become "specific dynamic" diseases. It seems that this definition, which was coined by Rubner to indicate the increased heat production after the administration of food, had best be restricted to the significance which it has already enjoyed for twenty years.

Dr. Francis G. Benedict, Boston: Probably no one has given more attention to the extraordinarily difficult problem of determining the average temperature of the human body than has Dr. Du Bois. I wonder whether the wholly remarkable correlation he finds between the temperature of the body and heat production is based on rectal temperatures or on the computed average temperatures. It is easily seen that the cell activity would have to be considered on the basis of the average body temperature rather than the local rectal temperature.

Dr. Walter M. Boothby, Rochester, Minn.: We have found that Du Bois' basal metabolic rate standards of normality based on the law of surface area are exceedingly accurate, and that the limit of normal variability is in a large majority of instances distinctly within plus or minus 10 per cent. of his zero. The consistency is exceedingly remarkable in a large series. We have made more than 23,000 determinations, and we hardly ever find a case with an abnormal basal metabolic rate that does not have a reasonable clinical explanation. In regard to what Dr. Crile said, it is obvious that, if he includes in his operative statistics for exophthalmic goiter the cases with normal basal metabolic rates, this factor, in addition to his beautiful technic, influences materially his mortality rate.

Dr. James H. Means, Boston: About the matter of body surface, the only thing I would like to say is that a study we have recently completed on the Du Bois, Benedict and Dreyer methods of judging of normality of basal metabolism shows that these three methods give almost identical results. I am often asked which method should be used. It does not matter. The result will be essentially the same. Dr. Crile spoke about the roentgen-ray treatment of goiter; I do not want to go into the subject of treatment. I do not want to say anything more now than what we have already said, which is that we believe that in certain cases there is more rapid improvement in clinical condition, and fall in rate of basal metabolism, pulse, etc., than one could expect as the result of spontaneous recovery. Spontaneous recovery exists, as everybody knows. The matter of recrudescence after

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roentgen-ray treatment has been mentioned. There are recrudescences. I have also seen recrudescences after surgery, after fairly complete operations, so that I do not believe the fact that recrudescences occur after roentgen-ray treatment means that the treatment has no place. In many cases it does no good; in others it does. The production of myxedema is the best possible proof that it may quiet the thyroid. It is easy to correct myxedema so arising by giving a little thyroid. As a matter of fact, in the cases we have seen the myxedema is transient, as I showed in one chart. I have seen several cases of myxedema following surgery.

Dr. Eugene F. Du Bois, New York: Dr. Benedict has sounded a much needed note of warning in stating that the simplification of technic has not simplified the understanding of the subject of basal metabolism or the interpretation of clinical results. Time saved by the modern technical improvements should be devoted to the study of textbooks on nutrition. As Dr. Benedict suggests, the increase in the metabolism in fever should follow the curve for the average body temperature rather than the rectal temperature. Practically, there is little difference between these two curves, except during sudden fluctuations. Furthermore, we are unable to determine the actual level of the average body temperature, and it is therefore necessary to use rectal readings. The manner in which the metabolism in fever follows the laws which govern the rate of chemical reactions lends support to the adoption of the term "metabolic rate" introduced by Dr. Plummer.

Dr. J. Earl Else, Portland, Ore.: During the last year and a half, I have been making a correlated study of the basal metabolic rate, pathologic findings, and clinical manifestations in toxic goiter. I have recently reviewed those cases in which the findings did not coincide, and have classified them into three different groups. In the first group are the errors in diagnosis. The patients had small goiters, with symptoms similar to those of mild toxic goiter, and a normal basal metabolic rate. These patients had other lesions, such as an early tuberculosis, or chronic infected tonsils, which produced the symptoms. I wish to take exception to the statement of Dr. Means relative to the value of basal metabolic studies. In the borderline cases, the basal metabolic rate is very important in diagnosis. The second group includes cases of toxic goiter in the stage of remission. Clinically, the patients show evidences of toxic goiter because, as has been shown experimentally, symptoms are present for a considerable period of time after the injection of thyroxin, while the basal metabolic rate remains elevated only for a comparatively short period of time. The third group includes cases of toxic goiter in which recovery has occurred so far as the thyroid and the excess secretion of thyroxin are concerned; but, on account of the patient having

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received an excessive amount of thyroxin over a long period of time, permanent lesions have been produced in the heart muscle, in the nervous system, behind the eyeball, and elsewhere, so that the patient still has a damaged heart, tremor and exophthalmos.

Dr. A. E. Rousell, Philadelphia: I disagree with the speaker who minimized the value of estimating the metabolic rate. Many cases of hypotension are unrecognized. Some of them, with edema and the presence of albumin and casts in the urine, will necessitate the estimation of the basal metabolism for a correct diagnosis, just as the study of blood chemistry is necessary in various forms of nephritis. The study of basal metabolism is an important adjunct to the practice of medicine, as are other methods of precision and, just like these other methods of precision, it has its limitations. I have been particularly interested in the fact of the decrease of the metabolic rate under the use of the roentgen ray. I have reported the marked improvement and cures that have existed for as long a period as four or five years in cases of toxic goiter treated by intensive doses of roentgen rays. Probably, the lighter doses produce just the opposite effect. Here the question is to produce necrosis, as one speaker represented the fact of producing myxedema is the best expression of the fact that the roentgen-ray treatment of toxic goiter is of extreme practical value.

Dr. Henry S. Plummer, Rochester, Minn.: The papers on this program were not supposed to deal with therapeutics. The authors have touched on the effects of roentgen-ray treatment, the excision of the thyroid, and they have discussed some of the relations of basal metabolism to fever and their application in clinical medicine. However, this was done largely from the point of view of basal metabolism, and it seems desirable to avoid diverging into the subject of the relative merits of therapeutic measures in the treatment of goiter. It is the obligation of every one interested in thyroid surgery to avoid the error of accepting basal metabolism as an index of the operability of the patient. It is the status of the patient relative to basal metabolism that is of much significance in determining operability in a case. It is the most fundamental measurement of the patient's condition. We have never seen, in the thyroids of pregnancy and adolescence, any evidence of the diffuse hypertrophy of the degree that is present in exophthalmic goiter and sometimes in the thyroids of laboratory animals. It seems probable that there is a relatively high rate of exhaustion of thyroxin during pregnancy and adolescence. Accepting this, a slight elevation of the basal metabolism during the period of pregnancy and adolescence, if present, does not necessarily indicate an elevation in the amount of thyroxin in the tissues. While it is possible that there are some other hyperthyroid states, we have not absolutely definite knowledge of any except that

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which follows the administration of thyroxin and those associated with adenomatous thyroids and exophthalmic goiter. The conservative stand at present is to assume that an individual having a normal basal metabolism is neither hypothyroid nor hyperthyroid: There is considerable evidence to suggest that there is rarely a short phase at the beginning, during the course of the disease, or following thyroidectomy for exophthalmic goiter in which the basal metabolism is normal, and a syndrome attributable to a perversion of the thyroid secretion is present. If true, we have no reason to believe that it often involves the question of differential diagnosis in cases in which the syndrome suggests hyperthyroidism, but in which the basal metabolism is normal. We have seen a large number of patients having relatively little complaint, no definite pathologic findings, and a basal metabolism ranging from 10 to 15 per cent. A study of this group indicates that these cases, although we cannot definitely classify many of them, cannot be considered up to the normal standard physiologically.

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CLINICAL STUDIES OF DRUGS OF THE "DIGITALIS SERIES"

III. APOCYNUM AND CONVALLARIA *

H. M. MARVIN, M.D.
AND
PAUL D. WHITE, M.D.
BOSTON

The treatment of heart disease by drugs other than digitalis is apparently a fairly widespread custom. The drugs commonly employed are those grouped by textbooks [1] as members of "the digitalis series." They include strophanthus, squill, apocynum, convallaria, adonis, oleander, hellebore and euonymus.[2] It has been our attempt, in the investigation here reported, to determine what foundation, if any, there may be for the use of apocynum and convallaria in the treatment of heart disease, either alone or in conjunction with one of the preparations of digitalis. The study is a continuation of that carried out on the tincture of squill, which was reported last year.[3]

* From the Massachusetts General Hospital and the House of the Good Samaritan, Boston.

* The previous papers of these studies are: White, P. D., and Satler, R. R.: The Effect of Digitalis on the Normal Human Electrocardiogram, with Especial Reference to A-V Conduction, J. Exper. M. **23**: 613 (May) 1916. White, P. D.; Balboni, G. M., and Viko, L. E.: Clinical Observations on the Digitalis-Like Action of Squill, J. A. M. A. **75**: 971 (Oct. 9) 1920.

1. Cushny, A. R.: Pharmacology and Therapeutics, Ed. 3, Philadelphia, Lea & Febiger, p. 375. Sollman, Torald: Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1917, p. 382.

2. Cactus grandiflorus is not included in any texts consulted by us, but it appears to be in fairly general use in the treatment of heart failure. That cactus is devoid of all demonstrable action on the heart rate, blood pressure and respiration has been conclusively demonstrated by many observers, and it did not seem worth while to use this substance for clinical studies (Cactus Grandiflorus, Report of the Council on Pharmacy and Chemistry, J. A. M. A. **54**: 888 [March 12] 1910, containing summary of work to date, with references. Lyon, E. P., and Qualls, G. L.: Experiments with "Cactina" and "Cactin," ibid. **55**: 455 [Aug. 6] 1910: Hatcher, R. A., and Bailey, H. C.: Cactus Grandiflorus, ibid. **56**: 26 [Jan. 7] 1911).

3. White, P. D.; Balboni, G. M., and Viko, L. E.: Clinical Observations on the Digitalis-Like Action of Squill, J. A. M. A. **75**: 971 (Oct. 9) 1920.

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APOCYNUM

Apocynum cannabinum, or Canadian hemp, is a plant which has been used medicinally in this country for about a century, having been introduced to the profession by Knapp [4] in 1826. He reported nineteen cases in which the extract of the plant had been given to provoke vomiting, diarrhea or sweating, with apparently a high degree of success. Knapp first recorded its action on the pulse; having taken a dose of 30 grains of the extract, he noted that his pulse fell from 70 to 50 in one hour, and to 45 in two hours. From 1830 to 1900, one may find a considerable number of references in medical literature to the use of this drug, most of them being favorable reports of its diuretic or emetic action.[5] Acceptable scientific work on the subject of its action, however, is strikingly absent, although Murray,[6] in 1889, reported observations showing that its diuretic action was limited to cases of edema due to heart disease, being absent in cases of nephritic edema. In 1904, Wood [7] reported a study conducted on animals which showed the drug to be possessed of a stimulating action on the cardio-inhibitory center and a constrictor action on the blood vessels. In 1910, Dale and Laidlaw [8] isolated a crystalline active principle, cymarin, with which they conducted careful experiments on warm-blooded animals. They concluded that "cymarin has an action which is like that of digitalis in all respects, but is not cumulative." Beco and Dossin [9] have recently reported further studies of cymarin,

4. Knapp, M. L.: Dissertation on the Properties of Apocynum Cannabinum, Am. M. Rev. & Jour. **3**: 194, 1826.

5. Dabney, T. S.: Apocynum, the Vegetable Trocar, Therap. Gaz. **14**: 730, 1898. Lowrey, J. H.: Apocynum Cannabinum, New York M. J. **60**: 472, 1894. Glinski, J., quoted in New York M. J. **60**: 320, 1894.

6. Murray, G. R.: The Physiological Action and Therapeutic Value of Apocynum Cannabinum **5**: 585, 1889.

7. Wood, H. C., Jr.: A Study of Apocynum Cannabinum, J. A. M. A. **43**: 1953 (Dec. 24) 1904.

8. Dale, H. H., and Laidlaw, P. P.: The Action of an Active Principle from Apocynum, Heart **1**: 138, 1909-1910.

9. Beco, L., and Dossin, F.: Experimental Research on the Physiologic Cardiovascular Action of the Active Principle of Apocynum, Arch. d. mal du cœur **13**: 376, 1920.

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in which dogs were used. Other reports which we have been able to find seem to possess chiefly historic interest.[10]

METHOD OF STUDY

As one purpose of our investigation was to compare the action of the selected drugs with that of digitalis in the same cases, we chose only the cases in which digitalis acts best, namely, cases of heart disease complicated by auricular fibrillation. We have thus avoided the possibility of controversy regarding the action of digitalis-like drugs in hearts with normal rythm. Among cases of auricular fibrillation, however, no selection was made; cases were taken as they came to the hospital, without reference to preceding history or underlying cause. In other words, in any case in which digitalis would ordinarily have been administered, either apocynum or convallaria was given first. Patients were allowed to remain in bed without medication for several days, or as long as there was definite clinical improvement or slowing of the heart rate. They then received apocynum or convallaria for a sufficiently long period to demonstrate the action or lack of action of the drug. It was then discontinued. After allowing a lapse of time sufficient for the excretion of the tested drug, each patient was given digitalis. Results which admit of fair comparison were thus obtained. During the time of administration of the drug, and until discharge, daily observations were made by the same observer at the same hour, regarding the rate of the heart (apex), pulse deficit, edema (subcutaneous, hydrothorax, ascites, etc.), diuresis, cyano-

10. Hurd, E. P.: New York M. J. **22**: 281, 1882. Griscom, J. H.: Observations on Apocynum Cannabinum, Am. J. M. Sc. **12**: 55, 1833. Schmiedeberg, O.: Arch. f. exper. Path. u. Pharmakol. **16**: 149; abstr. Therap. Gaz. **4**: 147, 1883. Sokoloff, D. A.: On the Action of the Root of Apocynum Cannabinum on the Heart and Vascular System in Warm-Blooded Animals, Ejenedelnaia Klinitcheskaia Gazeta, Nos. 25-26, p. 507, 1888; abstr. Med. Chron. **8**: 466, 1888. Gray, R. B.: Apocynum Cannabinum: Its Use by American Indians, New York M. J. **60**: 759, 1894. Kimball, J. P.: Apocynum Cannabinum: Its Use in Snake Bites, ibid. **61**: 21, 1895. Woodhull, A. A.: Apocynum Cannabinum, a Diuretic Plant, Brit. M. J. **2**: 1714, 1897.

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sis, cough, hemoptysis, precordial pain, palpitation, dyspnea, orthopnea, anorexia, headache, and any particular sign or symptom which individual patients might display. Electrocardiograms were taken daily during the administration of the tested drug, less frequently during the "waiting period," between the administration of that drug and digitalis, and always before, during and after digitalis administration. All patients had also daily determinations of the vital capacity of the lungs. (Exceptions are mentioned below.) As digitalis has a characteristic effect on the electrocardiogram, in which it causes inversion of the T deflection in Lead II, and definite slowing of the ventricular rate in cases of auricular fibrillation, it was thought that we might obtain graphic evidence of the cardiac action of these drugs, if they were possessed of any.

The preparation of the drug used in this study was the fluidextract. Three different specimens were obtained from three pharmaceutic houses, and all of them were tested on frogs.[11] This was done under the direction of Dr. Worth Hale, of the department of pharmacology of the Harvard University School of Medicine. Tested in this manner, the drug was found to have the frog-unit strength indicated in Table 1.

TABLE 1.—FROG-UNIT STRENGTH OF APOCYNUM *

Parke-Davis	fluidextract, 0.000225	c.c. per gram of body weight
Eli Lilly	fluidextract, 0.0002	c.c. per gram of body weight
Sharpe & Dohme	fluidextract, 0.0002	c.c. per gram of body weight

* Figures refer to the amount of drug required to cause systolic arrest of the heart in one hour.

11. While this article was in course of pubication, Dr. R. A. Hatcher kindly determined the cat unit strength of the specimens of apocynum and voncallaria which were used in our studies. The following quotation from Dr. Hatcher's report is of considerable interest: "The apocynum is about thirty times as active as an average good specimen of digitalis tincture; that is, 0.035 c.c. of the fluidextract is equal to a cat unit. This agrees very closely with the test on frogs (the fluidextract being ten times the strength of the tincture). The fluidextract of convallaria is about forty times as active as a good specimen of tincture of digitalis, according to my test, 0.25 c.c. being equal to one cat unit. This would indicate that it is about 30 per cent. more active by the cat test than by the frog test. Each of two cats received oral doses of 0.7 c.c. of the fluidextract of apocynum per kilogram of weight through a stomach tube (20 cat units per kilogram). They vomited after twenty-seven and thirty-four minutes, respectively; one of them vomited many times. Both showed either diarrhea or intestinal evacuation."

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It is to be noted that the figures in Table 1 are in terms of the fluidextract; the strength of the tincture will be represented by figures ten times as large. It is therefore obvious that the action of tincture of apocynum on the frog's heart is almost precisely three times as powerful as that of the official tincture of digitalis.

DOSAGE

The dose recommended for the fluidextract is 1 c.c. In our first few cases, we began with this dose, but found that it caused intense nausea and prolonged vomiting in every case; with a single exception, vomiting occurred within thirty minutes of such a dose. A routine dose of 0.5 c.c. gave almost the same effects, so it became our practice to administer the drug in doses of 0.1c.c. for each 30 pounds (13.6 kg.) of body weight, such dose being given in gelatin capsules three times a day. In cases in which quick action seemed desirable, we began with one dose, slightly larger than would be indicated on the basis of body weight, and then continued with the calculated amount three times a day.

RESULTS

We have studied the action of apocynum in the manner indicated in twelve cases of heart disease with auricular fibrillation, and one case of heart disease with auricular flutter. Three of these patients were in the House of the Good Samaritan, and they did not have daily electrocardiograms or vital capacity determinations. The twelve cases with fibrillation included three cases with exophthalmic goiter, in two of which the fibrillation seemed to be associated with the thyroid condition; in the third, there was a definite history of repeated rheumatic attacks preceding the development of the hyperthyroidism. These three cases form a special group as regards the response to treatment with apocynum.

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Production of Heart Block; Clinical Improvement.—In the nine cases of fibrillation not of thyroid type, the action of apocynum was marked by a quick reduction in the apex rate of the heart, a diminution in the pulse deficit, diuresis in all cases in which there was edema, and simultaneous improvement in the general clinical condition. Of the three cases associated with hyperthyroidism, two responded by a slight drop in the heart rate; the third resumed normal rhythm several days after the drug was started, although auricular fibrillation again made its appearance about ten days later. In none of these three cases was there any clinical improvement whatever. In the one case of heart disease complicated by auricular flutter apocynum acted in the manner which is typical of digitalis: fibrillation appeared within several hours of the first dose of the drug, which was then discontinued, and normal rhythm was resumed on the second day thereafter.[12]

Nausea and Vomiting.—In eleven of the twelve cases cited, there was intense nausea and vomiting. It was the appearance of these symptoms which necessitated the withdrawal of the drug in almost every instance. The nausea was of a particularly severe character, often not relieved at all by the vomiting, which was a constant accompaniment. It was so marked as to overshadow and obliterate the memory of the drug's good effects in every patient. It has been the impression of all of us who have watched these cases that the nausea and vomiting following the administration of apocynum are more severe than the same symptoms following overdosage with digitalis.

Duration of Action.—The action of apocynum on the heart was manifested only so long as it was given three times a day. In all cases, signs and symptoms which had disappeared under its use began to reappear

12. This patient has been seen once since her discharge from the hospital, at which time she showed auricular fibrillation.

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Fig. 1 (Case 8, apocynum).—Cardiosclerosis, right bundle branch block: *a*, Lead II, just before apocynum was started; ventricular rate, 140; T wave positive and averages 0.1 millivolt in height. *b*, Lead II, three days later; rate, 90; T wave diphasic, averaging minus 0.2 millivolt and plus 0.1 millivolt. Q R S complex shows marked increase in ampitude. Total amount of apocynum, 4 c.c. (In this and the succeeding electrocardiograms, distances between ordinates represent 0.2 second; between abscissas, 10^{-4} volt.) The change in level of the string indicates a change in potential of 1 millivolt of current, and is inserted to show standardization of string tension.

Fig. 2 (Case 3, apocynum).—Rheumatic heart disease, mitral stenosis. *a*, Lead II, taken at 9 a. m., before apocynum. (Inversion of 2 due to digitalis taken the previous week.) Rate, 110; T wave inverted. (Minus 0.1 millivolt.) *b*, Lead II, taken at 6 p. m., after two doses of apocynum, 1 c.c. each. Rate, 84; T wave more deeply inverted (Minus 0.25 millivolt). *c*, Lead II, taken five days later, after digitalis 1.2 gm. Rate, 84; T wave inverted (minus 0.25 millivolt).

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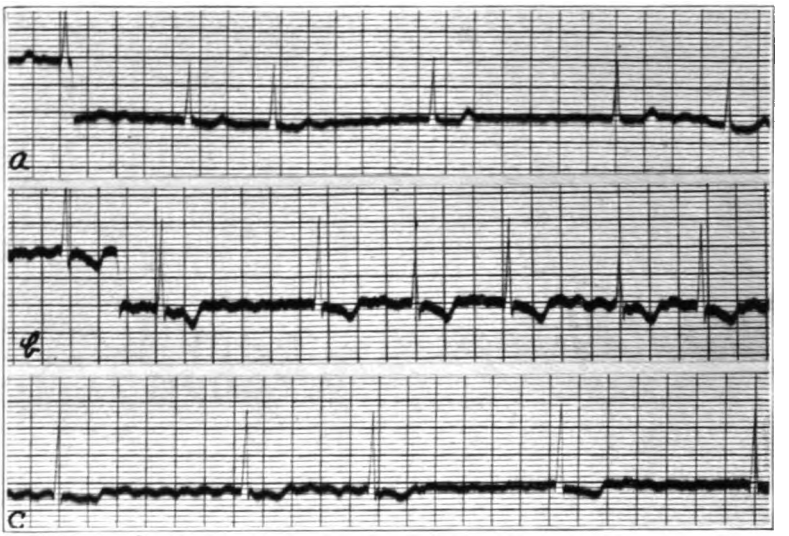

Fig. 3 (Case 5, convallaria).—Rheumatic heart disease, mitral stenosis: *b*, Lead II, taken three days after starting convallaria; shows deep inversion of the T wave (minus 0.3 millivolt); total amount of drug, 30 c.c. *a*, Lead II, taken six days after *b* (six days after stopping convallaria), showing that the normal wave in this patient is positive (plus 0.1 to 0.2 millivolt). *c*, Lead II, taken six days after *a*, showing inversion from 1.3 gm. of digitalis (minus 0.15 millivolt).

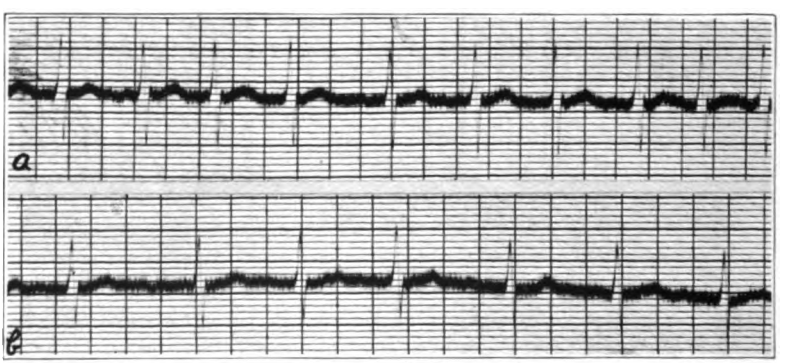

Fig. 4 (Case 12, convallaria).—Cardiosclerosis: *a*, Lead II, taken before starting convallaria; rate, 120; T wave positive (plus 0.15 millivolt). *b*, Lead II, after seven days of convallaria, total dose of 105 c.c.; rate, 84; T wave still positive (plus 0.1 millivolt).

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within forty-eight hours of its discontinuance, and in most cases there was a distinct rise in the rate of the heart within twenty-four hours after the drug was stopped.

Diuresis.—Seven of the twelve patients had edema at the time treatment was begun. Of the seven, five showed a definite decrease in the amount of edema which was demonstrable, and four of them showed a corresponding loss of weight. (The fifth patient was not weighed before treatment was started.)

Diarrhea.—This occurrred in only two cases; in one it was of moderate severity, in the other it was very severe, and continued for several days after the drug was stopped.

Blood Pressure.—Determinations were made in ten cases, usually every other day before, during and after the course of treatment. The most forceful pulsations were recorded. In no case was there a change in either systolic or diastolic pressure greater than 10 mm. of mercury, and in only two was the change as great as that.

Vital Capacity.—Eight patients of this series had daily vital capacity determinations. Six of them showed an increase during the period of administration of apocynum; these six patients all showed definite clinical improvement, the greatest improvement being shown in those patients whose vital capacity increased most. These results are in accord with those of Peabody and Wentworth,[13] but in none of our cases was the increase in vital capacity sufficient to be of importance in estimating the degree of clinical improvement.

Changes in Electrocardiogram.—Of the nine patients studied by means of daily electrocardiograms, three showed definite inversion of the T deflection in Lead II during treatment with apocynum; the same patients

13. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration, Arch. Int. Med. **20**: 443 (Sept.) 1917.

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showed an upright or flat T before and after treatment. One patient showed a decrease in the height of the T deflection (from 0.25 to 0.15 millivolts) without inversion; one resumed normal rhythm; one showed at entrance a T already inverted, probably from digitalis, which became slightly less so during the administration of apocynum. The two remaining patients showed no changes except definite slowing of the ventricular rate.

Comparison with Digitalis.—All of the twelve patients received digitalis after the effect of apocynum had been recorded. (In one case, the digitalis was taken after the patient left the hospital, but the results were carefully watched.) In every case, the favorable effect due to apocynum was exceeded by that due to digitalis; the lowering of the apex rate, the diminution in the pulse deficit, the diuresis, the clinical improvement, all took place to a greater degree, in a shorter time, without discomfort to the patient, and were more prolonged.

SUMMARY

The action of fluidextract of apocynum has been studied in a series of twelve cases of heart disease with auricular fibrillation and one case of heart disease with auricular flutter. The drug was given by mouth; clinical and electrocardiographic observations were recorded daily. If we exclude three cases of hyperthyroidism, the action of the drug on the heart in all cases, measured by clinical observations, was similar to that of digitalis. Its emetic action was pronounced in all cases except one, and occurred with the smallest doses that had any demonstrable effect on the heart. Its action on the heart, as judged by slowing of the rate, lessening of the pulse deficit, and improvement in symptoms, was extremely transient, disappearing in most cases within forty-eight hours, and in many within twenty-four hours, after it had been stopped. Blood pressure determinations showed no changes worthy of

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mention. Vital capacity determination showed in the majority of cases a slight increase following the administration of the drugs, the increase being coincident with, and roughly parallel to, clinical improvement. Electrocardiograms showed inversion of the T deflection in Lead II in three cases, and slowing of the ventricular rate in all. Digitalis administered subsequently in the same cases had a more pronounced beneficial effect, which lasted for many days and was not accompanied by the extreme discomfort which followed the use of apocynum.

Table 2 indicates the effect of apocynum on some of the more important signs and symptoms of heart disease.

REPORT OF CASES

CASE 3.—*Unfavorable Response to Apocynum.—History.*—A. B., a white married woman, aged 35, had had acute rheumatic fever seven years before. Her present illness began four years previously, with shortness of breath, palpitation, and swelling of the ankles, legs and abdomen. Since that time she had been under almost constant observation in hospitals. Only twice had she been sufficiently well to be out of bed. Signs of mitral stenosis had been present since the beginning of her illness; auricular fibrillation was first noted three years previously.

Physical Examination.—(The following signs have been noted at every examination for the last three years). There was marked cyanosis of lips and nails, and malar flush. The heart was enlarged, the apex impulse being palpable in the fifth space, 14 cm. to the left of the midsternal line; rhythm was absolutely irregular, and there was a loud first sound at the apex and a low pitched murmur, which extended through diastole. There were signs of considerable fluid below the angle of the right scapula; there was moderate ascites, and the liver was palpable at the level of the umbilicus. Considerable edema of the lower back, thighs, legs and feet was noted.

Rheumatic heart disease, mitral stenosis and auricular fibrillation were diagnosed.

Course and Treatment.—The patient had been taking digitalis. This was omitted for eight days, at the end of which time her dyspnea and palpitation were much worse, and the edema had increased. Apocynum was administered in varying doses, the average being 0.3 c.c., three times a day. There was a rapid fall (in twenty-four hours) in the rate of the

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heart, which remained fairly slow for six days, under small doses of the drug. During this time, there was some loss of the edema and of weight, and some clinical improvement, but the patient did not feel so well as when using digitalis. Apocynum was discontinued after a week because of nausea and vomiting; within three days the recurrence of symptoms demanded further treatment, and apocynum was again tried. It had less effect than before, but was continued for six days, when vomiting again made its omission necessary. Three days later digitalis was started, with rapid improvement in clinical symptoms and complete loss of the edema, which had never disappeared with apocynum. Two months later the whole experiment was repeated, in order to secure electrocardiograms. Again there was a rapid fall in the rate of the heart with apocynum, with practically no improvement in symptoms, and with severe nausea and vomiting. It had to be discontinued after two days. Digitalis was started three days later, its administration being marked by a rapid and permanent decrease in rate and diuresis, and by a decrease in or disappearance of all clinical symptoms. Electrocardiograms showed slowing and inversion of the T wave in Lead II.

CASE 8.—*Favorable Response to Apocynum.—History.*—G. L., a white man, aged 64, widower, cotton-mill spinner, had previously been in excellent health, and had had no acute infectious diseases. His present illness began about one year previously, with shortness of breath, palpitation and swelling of the ankles. These have been sufficiently severe to make him enter hospitals for treatment on two occasions. His present entry was his third. The chief complaint now was dyspnea and swelling of the ankles and abdomen.

Physical Examination.—The apex impulse of the heart was palpable 13 cm. to the left of the midline, in the 5th space; the right border of dulness was 3 cm. to the right. The sounds were faint and absolutely irregular in rhythm. There was a soft systolic murmur at the apex. There was a rate of 134, and a pulse deficit of 38. Signs of fluid were disclosed in both chests. There was flatness below the angle of the right scapula and, to a lesser extent, on the left. The liver was palpable at the level of the umbilicus. Slight shifting dulness was present in the flanks. Edema of legs and ankles was noted.

Cardiosclerosis, auricular fibrillation and right bundle-branch block was diagnosed.

Course and Treatment.—There was no change in the rate of the heart nor improvement in symptoms after three days of rest in bed. Apocynum was started on the fourth day in doses of 0.4 c.c., three times a day. There was little effect for two days; on the third, there was a rapid fall in the heart rate to about 60, the pulse deficit diminished, and diarrhea and

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diuresis commenced. During the succeeding four days there was steady clinical improvement; dyspnea, palpitation and edema entirely disappeared, and there was a loss of 12 pounds in weight. Nausea and vomiting occurred on the seventh day, after the full therapeutic effect had been obtained. Apocynum was then stopped. Six days later digitalis was started, because of rise in the apex rate to 100 per minute, and caused a rapid fall in the rate of the heart and a decrease in the deficit, but effected little improvement in symptoms, as there were practically none when it was started. Electrocardiograms showed inversion of T and considerable slowing. In view of the improvement with apocynum, this patient was instructed to take it at home, and report regularly to the cardiac clinic of the outpatient department for observation. For about one month he did quite well, although there was a slight increase in shortness of breath. Five weeks after his discharge from the hospital, however, it was necesssary to place him again on digitalis, as all his old signs and symptoms had begun to return. Since that time, he has done well on digitalis.

CASE 13.—*History.*—A. K., a white married woman, aged 44, had had rheumatism twenty years previously. Signs of mitral stenosis were first noted in the course of a routine examination ten years previously. For the last two years she had had dyspnea and palpitation on exertion, but it was never very severe until one week before. For the last week, palpitation, dyspnea and orthopnea had been marked and had not decreased with rest in bed.

Physical Examination.—There was slight cyanosis of the lips. The apex impulse of the heart was in the fifth space, 11 cm. to the left of the midline. The right border was not beyond the sternum. The rate was 190 and was regular. There was a loud bell-like sound accompanying the first heart sound all over the precordium. No murmurs were distinguished. There were signs of slight effusion in both chests. The liver was palpable, 3 cm. below the costal border. Slight edema of ankles was noted. The electrocardiogram showed auricular flutter, with 2:1 block.

The diagnosis was rheumatic heart disease; mitral stenosis; auricular flutter.

Course and Treatment.—Immediately after entrance, at 5 p. m., the patient received 1 c.c. of fluidextract of apocynum. At 10 p. m. the rhythm was absolutely irregular, and the apex rate was 142. The radial pulse could not be counted. The electrocardiogram, taken at 9 a. m. the following day, showed fibrillation. Apocynum was given twice on this day, in doses of 0.5 c.c. There was severe nausea and vomiting after the second dose, so it was stopped. On the second day thereafter, normal rhythm had been resumed, and the electrocardiogram showed a high P wave and an inverted T in Lead II. A few days later the T wave was upright.

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Action.—Apocynum in this case of auricular flutter had an action similar to that of digitalis in such cases. It first converted the flutter into fibrillation. It was then withdrawn, and normal rhythm was resumed in two days. There was suggestive evidence of the inversion of T in Lead II.

CONVALLARIA

Convallaria majalis, or lily of the valley, has been known in medicine for several hundred years. Laigre,[14] in 1903, refers to its use as early as 1580 by a French physician, who wrote concerning it: "The Germans use it much to fortify the heart, the brain, and other noble organs. They employ it also against palpitation." As far as one may judge from references to literature not now available, its use during the sixteenth and seventeenth centuries and a part of the eighteenth century was confined largely to cases requiring emesis or catharsis; but in 1770, according to Laigre, "the stimulating, diuretic and calming virtues of the plant in asthma due to cardiac trouble" were recognized by Ferrein. Since 1880, a large majority of all articles concerning its therapeutic use have emphasized its "truly remarkable diuretic properties," and at least one writer has pleaded for its universal adoption under the attractive caption: "Convallaria, the Vegetable Trocar." It is difficult to escape the conclusion that convallaria has been effective in causing diuresis in certain cases reported, but the literature is confusing because of the number of different preparations of the plant which have been employed. Thus, Moriquard[15] and Dellenbaugh[16] have recommended the infusion of the leaves, Germain See[17] preferred the aqueous extract of the whole plant; Hurd[10] used the fluidextract of the root, while Laigre[18] recognizes differences in the action of the two glucosids

14. Laigre, J.: Muget et suc de muguet, Revue de thérap. méd.-chir. **51**: 757, 1903.
15. Moriquard, G., and Jujol, G.: On the Diuretic Action of the Infusion of Lily of the Valley in Children, Progrès Med. **28**: 499, 1912.
16. Dellenbaugh, Z. P., quoted in New York Medical Record **28**: 196, 1882.
17. See, Germain: On Cardiac Hypertrophy, etc., Semaine méd., 1885, p. 3.

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contained in the plant, convallarin and convallamarin, and urges the use of these glucosids.

The official (N. F.) preparation in this country is the fluidextract of the root, and it is this preparation which was used in the present study.

The method of study has been given in detail in an earlier section of the paper, and need not be discussed again. The cases studied were selected in the same manner as those for the apocynum investigation, and were twelve in number, all of them being cases of heart disease complicated by auricular fibrillation. Of these twelve, three were cases of hyperthyroidism, but they did not form so distinct a group in this study as in the other. The remaining nine cases comprised five with rheumatic heart disease and four with cardiosclerosis.

It is readily seen from Table 3 that convallaria, tested on the frog's heart, possesses the same strength as apocynum and is approximately three times as powerfull as digitalis.[11]

TABLE 3.—FROG-UNIT STRENGTH OF CONVALLARIA *

Parke-Davis	fluidextract,	0.00025 c.c. per gram of body weight
Eli Lilly	fluidextract,	0.00025 c.c. per gram of body weight
Sharpe & Dohme	fluidextract,	0.00025 c.c. per gram of body weight

* Figure refers to the amount of drug required to cause systolic arrest of the heart in one hour.

The dose of the fluidextract recommended is 0.5 c.c.; the dose employed by us in almost all cases was as large as 5 c.c., three times a day, and in many cases as high as 10 c.c.; one patient actually receiving 15 c.c., three times a day. In the first few cases, we began treatment with the dose recommended, but finding it without demonstrable action, we increased it rapidly. In later cases, we began routinely with doses of 5 c.c., three times a day.

RESULTS

Production of Heart Block; Clinical Improvement.— In regard to the action of the drug, the twelve cases may readily be divided into two groups: those which

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responded with improvement, and those which showed no change whatever or actually grew worse. The first group is composed of two cases; the remaining ten fall into the second. The criteria used for estimating clinical improvement were those already mentioned: lowering of apex rate, diminution in pulse deficit, diuresis, and a decrease in such symptoms as dyspnea, cough, palpitation, insomnia, anorexia and headache, as well as the patient's sense of well-being, or the reverse. The two patients who showed clinical improvement were cases of cardiosclerosis without evidence of valve damage; in both, the action of the drug was similar to that of digitalis (given subsequently) except that one of them did not show inversion of the T deflection of the electrocardiogram. Heart block was produced in six cases. Further details are given in Table 4.

It is interesting to note the reasons for stopping the drug in the ten cases which did not show improvement. They are: slowing of the heart rate (without any improvement in symptoms), one; excessive diarrhea and abdominal pains, one; increase in signs and symptoms of heart failure, one; simple failure to improve, even with massive doses, one; failure to improve, plus nausea or vomiting, six.

Nausea and Vomiting.—As noted above, this occurred in a majority of the cases—nausea in nine, and vomiting in six. In no case was the nausea or vomiting so intense and distressing as that seen following the administration of apocynum.

Duration of Action.—The transient nature of the action of this drug is definite, but not so marked as in the case of apocynum. In several cases, there was an increase in the rate of the heart and recurrence of symptoms within twenty-four hours after the drug was withdrawn. The time elapsing between the stopping of convallaria and the administration of digitalis, however, averaged about three days for the whole series, the extremes being three hours, and seven days.

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Diuresis.—It is unfortunate that only two of our cases showed edema at the time of giving convallaria. In both of these, the edema was decreased, and in one it disappeared entirely. The latter case is the one which showed the greatest clinical improvement of the entire twelve.

Vital Capacity.—This was determined daily in nine cases, the other three being patients at the House of the Good Samaritan. In only six was there an increase of as much as 100 c.c. In the two patients who showed clinical improvement, the precentage of increase in vital capacity was greatest. No comparison between vital capacity increase and clinical improvement is possible in the remaining cases, because there was no clinical improvement.

Blood Pressure.—Blood pressure determinations (maximal beats) were made in seven cases in this series, readings being made at intervals of two days. Comparison of the figures before, during and after the period of convallaria administration shows that the greatest change was 10 mm. of mercury, which occurred in one case (a rise during the time the patient was receiving convallaria). This had returned to its previous level within two days. No other case showed a change in systolic or diastolic pressure greater than 4 mm., at any time.

Diarrhea.—This occurred in six of the cases, being slight in two cases, moderately severe in three, and very severe in one. As there had been no change whatever in the regimen of these patients, except the administration of convallaria, and as the diarrhea stopped promptly when the drug was withdrawn, it seems fair to conclude that there may have been a causal relation between the two.

Changes in Electrocardiogram.—Eight cases had daily electocardiograms, and of these, three showed a definite inversion of the T deflection in Lead II. Of

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the remaining five, two showed reduction in the ventricular rate, and three showed no changes whatever.

Comparison with Digitalis.—Of the twelve patients, ten received digitalis subsequently. (Two patients left the hospital against advice before receiving it.) In all ten cases, the administration of digitalis was followed by definite, prompt improvement, subjective and objective, showing that the failure of convallaria to act was not due to any peculiarity of the patients.

REPORT OF CASES

CASE 24.—*Unfavorable Response to Convallaria.—History.*—R. G., a white married woman, aged 50, had had acute rheumatic fever twenty-six years previously. For nineteen years she had had occasional attacks of precordial pain, and for fifteen years occasional edema of ankles and feet after standing. For three years she had suffered from increasing weakness, dyspnea and palpitation on exertion; also from a slight increase in frequency and severity of precordial pain. For the last four months she had grown steadily worse. Edema was constant, the abdomen had increased in size, and climbing stairs had become impossible.

Physical Examination.—The heart was enlarged, the apex impulse being visible and palpable in the fifth space, 12 cm. to the left of the midsternum, and the right border of dulness being 3 cm. to the right. There was no thrill The rhythm was absolutely irregular, apex rate 88; radial rate, 72. The first sound at the apex was loud and valvular; the second sound at pulmonic area was accentuated. There was a short, soft low-pitched middiastolic murmur heard at the apex. The lungs were clear. The liver edge was palpable 3 cm. below the costal border. Moderate edema of ankles and legs was noted.

The diagnosis was rheumatic heart disease; mitral stenosis; auricular fibrillation.

Course and Treatment.—Three days' rest in bed caused no slowing of the heart nor improvement in symptoms. On the fourth day, fluidextract of convallaria was started in doses of 5 c.c., three times a day. Diarrhea began after the second dose and abdominal pain after the third. There were eight loose bowel movements in twelve hours. Diarrhea was controlled by opium, and the administration of convallaria was continued. Vomiting occurred after the fourth dose, was repeated (four times) after the fifth, and again after the sixth, at which time abdominal pain again started. The drug was discontinued, but the diarrhea was not checked for five

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days, during which time the patient had constant and complete anorexia. The action of the convallaria on the heart was manifested by slowing of the ventricular rate. Electrocardiograms showed slowing and inversion of the T wave in Lead II (Fig. 3). One week after stopping convallaria, digitalis was started. The patient received 1.2 gm. of the leaf in two days, with marked beneficial effect, rapid drop in heart rate, and improvement in all symptoms. Electrocardiograms showed the typical digitalis effect on the T wave.

CASE 25.—*Favorable Response to Convallaria.—History.*—J. C. D., a white man, aged 61, single, a shoe-laster, had had no rheumatic infections. For fourteen years, he had suffered slight occasional precordial pain after exertion. Dyspnea was first noted two years previously, rapidly increasing to orthopnea. At the same time, edema of the lower extremities developed. He entered the hospital, where diagnoses given herewith were made. He remained two weeks, and responded well to treatment with digitalis. After discharge, he was able to work as a shoe-laster for about seven months, taking digitalis in small doses constantly. He had constant orthopnea and edema of the feet at night. When the supply of digitalis was exhausted, he became very dyspneic and edematous.

Physical Examination.—There was cyanosis of the lips and the heart was enlarged, the apex impulse being palpable in the fifth space, 12 cm. to the left. The right border of dulness was 3 cm. to the right of the midsternal line. The rhythm was absolutely irregular, the sounds were of poor quality, and there were no murmurs. A rate of 100, and a pulse deficit of 14 were noted. There were signs of fluid below the angle of the right scapula, and the liver edge was palpable 4 cm. below the costal border. Edema was present in the ankles and over the sacrum.

The diagonosis was: cardiosclerosis; auricular fibrillation; right hydrothorax.

Course and Treatment.—After three days' rest in bed, the patient had shown no improvement. The cough was extremely troublesome, dyspnea and orthopnea had not decreased, and the apex rate and deficit had shown no change. The edema was as marked as at entrance, and the weight was the same. On the fourth day, fluidextract of convallaria was started in doses of 5 c.c., three times a day, and continued without change or intermission for seven days. There was no appreciable effect for four days. On the fifth day, the heart rate was slower and the symptoms (cough and dyspnea) indicated a distinct improvement. Diuresis began at the same time. By the seventh day, the apex rate was 62; cough, edema, hydrothorax and dyspnea had entirely disappeared, and the patient had lost 14 pounds in weight. Electrocardiograms showed only slowing, and the T wave was not inverted (Fig. 4). Convallaria was discontinued for ten days, when a rise

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in apex rate and a return of slight dyspnea and cough made treatment necessary. Digitalis (leaves), 0.2 gm., three times a day, for two days, reduced the apex rate from 98 to 58, and gave complete relief from symptoms.

SUMMARY

The action of fluidextract of convallaria has been studied in twelve cases of heart disease complicated by auricular fibrillation. The drug was given by mouth in doses varying from 0.5 to 15 c.c., three times a day. It was followed by clinical improvement in two cases; in the remaining ten, it had no favorable action on the heart and circulation, and in several it caused unfavable symptoms which demanded its discontinuance. Nausea or vomiting occurred in nine cases; diuresis in the two patients who showed edema at the beginning of treatment. Diarrhea was noted in six cases, and was of moderate or marked severity in four. Blood pressure determinations showed no changes. Vital capacity was increased in six instances; in only three was the increase marked. In only two cases was there any evidence of a sedative action, and in one of these it was so slight as to be questionable. Electrocardiograms showed in three instances a typical digitalis-like inversion of the T deflection in Lead II. The action of the drug was very transient. Digitalis given subsequently to the same cases had a uniformly prompt and favorable action.

CONCLUSIONS

1. The results of clinical studies on the fluidextract of apocynum cannabinum indicate that the drug has, in some degree, a digitalis-like action in cases of heart disease with auricular fibrillation. Its possible usefulness in the treatment of heart failure, however, is markedly limited by the discomfort, nausea and vomiting which invariably follow its administration in doses sufficiently large to affect the heart.

2. In one case of auricular flutter, the administration of apocynum was followed within several hours by a

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change to auricular fibrillation. The drug was withdrawn, and normal rhythm was resumed two days later. So far as we are aware, this is the first case reported illustrating the action of apocynum in auricular flutter.

3. Similar clinical studies on the fluidextract of Convallaria majalis indicate that only in occasional cases does it have any favorable action on the heart in auricular fibrillation; even in these occasional cases, its action does not resemble that of digitalis in all details.

4. It would seem from our results that neither apocynum nor convallaria can be used as substitutes for digitalis. In our experience, digitalis has been characterized by quicker action, more pronounced effects, less discomfort, and more prolonged improvement, than are seen following either of the other drugs. We are convinced that both of these members of the digitalis series have no place in the rational treatment of heart failure.

The authors desire to express their appreciation of Dr. G. M. Balboni's cooperation and assistance and Dr. Hatcher's kindness in determining the cat-unit strength of the drugs.

ABSTRACT OF DISCUSSION

DR. ROBERT A. HATCHER, New York: A single study such as this increases our knowledge of apocynum and convallaria more than all of the work of the century preceding. I should like to call attention to the similarity of results to those obtained in our laboratory in one case, and the dissimilarity in the other. We found that massive doses of convallaria might be given orally without perceptible effects in some cases. This corresponds quite well with the observations just reported. Fifteen cubic centimeters of fluidextract of convallaria is equivalent in cardiac activity to 45 c.c. tincture of digitalis. That dose of convallaria was given several times in the course of a day. If this study will result in the dismissal of convallaria from the materia medica, the authors will have performed a great service. It is, of course, beyond question that many clinicians are not prepared to make such careful observations, and that they will often confuse the results of the drug with cardiac disease; and, failing to observe an improvement with ordinary doses, they will push the administration of a drug of this type until the patient dies of digitalis poisoning. In other cases in which they

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rely on the drug, the patient goes on to death through the want of any relief at all. In the case of convallaria the results here reported clinically are in harmony with those in the laboratory of pharmacology. As to apocynum, the difference is more apparent than real. In some cases the nausea occurs in a few minutes often the administration of a modern dose of apocynum, and there was no greater effect in many cases from ten times as much because rapid emesis or purgation prevented further absorption. When emesis fails to occur, rapid absorption of the toxic dose may take place. While it is safe to use such drugs when they are observed as carefully as in this case, they are dangerous in the hands of the clinician not prepared to make these observations. I hope we will dismiss from the materia medica, convallaria and apocynum, and the other members of this group, which have no apparent advantage over digitalis.

Dr. Paul D. White, Boston: It is very often of interest to compare the action of different drugs on the same subject. One can form conclusions of great value, when the individual variations may be dispensed with in this way. One of the subjects now reported by Dr. Marvin was also a subject of our squill investigation last year. She was a woman, aged 36, who had rheumatic heart disease and auricular fibrillation. She received 1 gm. digitalis by mouth at one dose. The result showed marked objective and symptomatic improvement. The pulse became much slower than before the large dose with less deficit. Toxic effects were negligible. The apical pulse rate dropped from 130 to 55 within twenty-four hours. This showed very strikingly the digitalis effect. Several weeks later, tincture of squill was administered, 2 c.c., three times daily. During the next five days she received 32 c.c. of tinture of squill with absolutely no effect until, finally, nausea occurred. There was no increase in urine output; marked pulse deficit persisted; the apex rate was 138; there was no drop in pulse rate from squill. The patient was symptomatically worse. Later on in other patients, we found it necessary to increase the dose of tincture of squill to 2 or 4 drams in order to get digitalis action. This patient received fluidextract of apocynum. A single dose of 1 c.c. was promptly vomited. Another dose of 1 c.c. was given in three hours, and a second dose of 0.36 c.c. three hours later. At the time of the first dose, the apex rate was between 160 and 170; the radial rate was 70. The patient was suffering from precordial pain, extreme palpitation of the heart, marked dyspnea, and a sense of fulness in the abdomen. There was slight cyanosis of the hands, lips and face. Four and a half hours after the last dose of apocynum, the pulse rate was 60 at the apex and wrist, and all of the symptoms mentioned had disappeared. However, the drug caused intense nausea and persistent vomiting followed. On another occasion 13.6 c.c. of the fluidextract convallaria was given in six days.

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Considerable subjective improvement resulted but nausea and vomiting necessitated stopping the drug. The apex pulse rate had dropped from 118 to 80, and the pulse deficit from 28 to zero. The effect was very transient, the recurrence of tachycardia, etc., requiring the administration of digitalis within three days.

Dr. Cary Eggleston, New York: I want to call attention to a rather remarkable feature in the observations on apocynum, namely, the question of the apparent dissociation between its emetic action and its cardiac action. It is well known that all of the digitalis bodies are capable of producing emesis and virtually solely after absorption by central stimulation. In the case of digitalis, while emesis is a frequent occurrence, it almost never occurs so early as to interfere with the development of therapeutic effects. In the case of apocynum it was striking that in almost all instances emesis developed very early and with much smaller doses than were required to produce therapeutic effects. Drs. Marvin and White show that even though apocynum was apparently rapidly absorbed from a single dose, the amounts required to produce therapeutic effects were very much larger, in terms of activity, than those required in the case of digitalis. They found that an average of 9 c.c. of fluidextract of apocynum was required to produce therapeutic effects. This, when reduced to terms of activity, corresponds to 270 c.c. of tincture of digitalis as the average dose required, which is approximately ten times the average dose; so that even when the drug is given in doses which do not promptly produce vomiting, and even though, as indicated by the vomiting, its absorption is rapid, the development of its action on the heart is very slow. It is to be hoped that this work will finally put a quietus on the use by physicians everywhere of either apocynum or convallaria.

Dr. Harold M. Marvin, Boston: In trying to investigate the extent to which these drugs are now employed clinically, one of our methods was to request a report of yearly sales from some of the leading pharmaceutical houses. Three of them were kind enough to send us their figures. One reported that sales had fallen off materially; two reported that there had been but little reduction in the annual sales, which amounted to about 15,000 pints of the fluidextract.

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THE TREATMENT OF CARBON MONOXID POISONING

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Carbon monoxid poisoning is so common in modern communities that the death rate on its account is comparable to that from diseases which, if not the commonest, rank close after the commonest. The chances for any one of us dying by carbon monoxid asphyxia are greater than by nearly any other, except one perhaps, of what used to be considered unnatural modes of death. The therapeutics of carbon monoxid asphyxia are therefore important.

An earnest protest is, however, needed just now against the almost hysterical attitude which certain elements of the lay public, and even some medical writers, also, are taking on this subject. After all, not so many people are asphyxiated by carbon monoxid as by water. But the fear of drowning does not close the bathing beaches or stop the ferries and excursion steamers. Automobilists are usually healthy, but they all inhale more or less carbon monoxid, if not from their own car, at least from the car ahead.

Common sense and common experience, as well as thoroughly grounded scientific evidence, indicate that the idea that carbon monoxid is toxic and cumulative in amounts below one part of the gas in 10,000 parts of air is without foundation. With carbon monoxid asphyxia, as with water asphyxia, the amount of the asphyxiant and the duration of its action are of critical importance. Resuscitation from drowning and resuscitation from carbon monoxid differ markedly in certain features. But in each the ends aimed at are fundament-

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ally the same, namely, elimination of the asphyxiant, supply of oxygen to the blood and tissues, and restoration of breathing.

A STANDARD OF EXPOSURE

We and our associates [1] have recently worked out a standard for exposure to carbon monoxid which may be expressed by the rule: Multiply the time of exposure in hours by the concentration of the gas in parts per 10,000 of air. If the product equals 3 or less there is no appreciable physiologic effect. If it equals 6, there is sometimes slight malaise. If it equals 9, a headache with some nausea is produced in most people. If it equals 15, the conditions are dangerous for anything beyond brief exposure. If it is more than 15, they are extremely dangerous even for brief exposure.

Our investigations along this line were carried out under the U. S. Bureau of Mines, for the New York and New Jersey Tunnel Commissions. The results show that if the proposed tunnel for automobiles under the Hudson river is ventilated as fully as is proposed (the carbon monoxid is not to rise above 4 or 5 parts in 10,000 of air, and the time for passage will be about a quarter hour, or a half hour for trucks), its use will cause no injury whatever to the health of passengers using it daily.

On the other hand, owing to the defects of carbureters, or rather to the way they are usually adjusted, as the investigations of Mr. A. C. Fieldner and his associates in the bureau of mines have recently shown,[2] an automobile engine may produce 1 or even 2 cubic feet or more of carbon monoxid per minute. Thus, a car warming up in a small garage (10 by 10 by 15 or 20 feet, that is 1,500 to 2,000 cubic feet), with doors closed on a cold morning, makes an atmosphere dangerous to life within five minutes or less time. The

1. Henderson, Yandell; Haggard, H. W.; Teague, M. C.; Prince, A. L., and Wunderlich, R. M.: Report of Tunnel Gas Investigation, to be published by the U. S. Bureau of Mines and, in brief, by the Journal of Industrial Hygiene, July, 1921.

2. Fieldner, A. C.; Straub, A. A., and Jones, G. W.: Jour. Soc. Automotive Engineers, April, 1921, and Bureau of Mines Reports of Investigations, March, 1921, Serial No. 2225.

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frequency of fatalities under such conditions in the winter months nowadays affords a gruesomely satisfactory and practical confirmation of our theoretical deductions. Adjustment of carbureters to give a thin mixture decreases, and a rich mixture increases, carbon monoxid production. Gasoline vapor itself, except in high concentration, has little pharmacologic effect.[3] In high concentration it acts like a very bad grade of ether, inducing anesthesia and convulsions.

We have mentioned these facts regarding the problem of vehicular tunnel ventilation and regarding the small closed garage, because the contrast is instructive. The safety assured in the tunnel and the danger occurring in the garage illustrate the point that carbon monoxid is not, like lead, for instance, an accumulating poison. It is rather an asphyxiant like water; taken occasionally and in small amounts it is almost as harmless. Its use is not, however, as yet encouraged by a constitutional amendment.

UNION OF CARBON MONOXID WITH HEMOGLOBIN

Carbon monoxid is not in any degree whatever a tissue poison. The nervous disorders and lesions following asphyxia are due to the anoxemia and not to a direct action of carbon monoxid on the cells in the brain and heart. On this point the evidence now available is, in our opinion, absolutely conclusive. We shall mention here only one fact to illustrate it. One of us[4] has recently tested the question by the method of tissue culture. Pieces of living and developing brain of a chick are suspended in a hanging drop of chicken plasma at body temperature. Some of these hanging drops are placed in an atmosphere 79 per cent. carbon monoxid and 21 per cent. oxygen, while the controls are in air, which is 79 per cent. nitrogen and 21 per cent. oxygen. The former grow and develop quite as actively as the latter, although the carbon monoxid is 100 to 200 times as strong as would kill a chick by combining with

3. Haggard, H. W.: J. Pharmacol. & Experi. Therap. 16: 401 (Dec.) 1920.
4. Haggard, H. W.: Am. J. Physiol., to be published.

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its hemoglobin and thus asphyxiating it. In other words, the whole toxicity of carbon monoxid depends on its union with hemoglobin.

TOXIC ELEMENTS IN ILLUMINATING GAS

It should be added, however, that illuminating gas and even exhaust gas of automobiles using some adulterated gasolines, contain other substances, for example, benzene (benzol), which are tissue poisons. Accordingly, by the same method it was found that illuminating gas, even in comparatively low concentration, kills the fragments of chick brain. It also kills flies and other insects which, having no hemoglobin, are absolutely immune to carbon monoxid. Investigations in this laboratory indicate that it is the benzene and related substances in illuminating gas, and not carbon monoxid, which is responsible for the anemia sometimes occurring in persons constantly around leaking gas fittings. These substances are powerful respiratory stimulants, thus augmenting the rapidity of absorption of carbon monoxid in acute and rapid poisoning. It seems to us quite possible, and even probable, that our city gas companies could supply us with cheaper gas, with more profit to themselves, and with fewer deaths from misuse of their product, if the laws and regulations allowed them to supply a gas free from such illuminants as benzene.

THERAPEUTIC DATA

Confining our attention to carbon monoxid, since it is still decidedly the chief toxic substance in illuminating gas, in exhaust gas, and in all ordinary forms of smoke, we may take as our starting point for therapeutics these dota:[5] (1) The whole effect of carbon monoxid is due to its combining with hemoglobin and excluding oxygen. (2) Its combination with hemoglobin is entirely and readily reversible. Red cells which have taken up a considerable percentage of their

5. Henderson, Yandell: Carbon Monoxid Poisoning, J. A. M. A. 67: 580 (Aug. 19) 1916.

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capacity for carbon monoxid and have given it off again are as good as before. At the end of our tunnel investigations, all of us had many red cells circulating in our blood, and rendering efficient service, which had been through this process repeatedly. We probably have some of them yet, for the experience does not shorten their lives; it rather encourages a polycythemia. Evidently the treatment designed to stimulate the formation of new red cells by bleeding and the infusion of saline solution lacks logical foundation.

TREATMENT IN CARBON MONOXID ASPHYXIA

It would seem from these facts, at first sight, that inhalation of oxygen would be indicated as the proper treatment for carbon monoxid asphyxia. A close fitting mask and valves would be needed for the administration, for when oxygen is passed through an inverted funnel held over the face, the patient gets practically none of it.

But even with a good inhaler, and a well-fitting mask and valves, the therapeutic results are, in fact, not much better than with fresh air. The patient recovers or dies, according as the injury wrought during the asphyxia, and the remedial forces of nature may decide. Doubtless it helps somewhat to keep the patient warm, occasionally also after brief and very acute asphyxia, life may be restored by artifical respiration, most readily by the prone position or Schäfer method.[6] But in most cases the physician might as well telephone, as one did, "Open the windows, and I will be up after breakfast."

There is urgent need of some specific means of treatment, something to have at hand at all city fires for immediate application to firemen overcome by smoke; something for use at coal mine explosions, and as part of every ambulance. But until quite recently the key to unlock this problem was lacking. Now we have it. It lies in the application of an idea which one of

6. Henderson, Yandell: Resuscitation Apparatus, J. A. M. A. 67: 1 (July 1) 1916.

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us (Y. H.)[7] brought forward many years ago in another connection, but which most physiologists then rejected Indeed, it is only quite recently that its application to the problem before us has become clear.[8]

COURSE OF EVENTS

When a man is slowly asphyxiated by illuminating gas, or a dog is asphyxiated in the laboratory, the course of events is as follows: As the blood gradually takes up more and more carbon monoxid, the increasing oxygen deficiency induces an augmentation in the volume of air breathed per minute. This, of course, augments the absorption of the gas. But it has also another effect. It washes carbon dioxid out of the body.[9] Now the normal stimulus for breathing is the carbon dioxid, which the blood carries to the respiratory center. A time comes, sooner or later, when the lack of carbon dioxid has progressed to a point at which respiration stops, for lack of this stimulus. This is the way in which death has occurred invariably in our experiments.[10]

If, however, before death, but in profound coma, the subject is removed from the gassing chamber to fresh air, but is not further treated, the condition seen during the next half or three quarters of an hour is one of extremely feeble breathing. If small samples of blood are drawn and analyzed for carbon monoxid, it will be found that very little of the gas is eliminated during this time. The condition of acute asphyxia continues and is exacerbated by the poor respiration.

Meanwhile the carbon dioxid in the blood, starting from the low figure to which it has been brought by the earlier hyperpnea, gradually reaccumulates to some extent. It is only as this reaccumulation of carbon dioxid develops that respiration gradually returns toward the normal. It may then become again exces-

7. Henderson, Yandell: Amer. J. Physiol. **24**: 66-85 (April) 1909.
8. Henderson, Yandell and Haggard, H. W.: J. Pharmacol. & Exper. Therap. **16**: 11 (Aug.) 1920.
9. Haggard, H. W., and Henderson, Yandell: J. Biol. Chem., July, 1921.
10. Haggard, H. W.: Am. J. Physiol., August, 1921.

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sive, as is frequently seen in patients; for the loss of carbon dioxid has caused also a loss of alkali from the blood. This alkali must be restored by the body itself, rather than from without. But until it is restored, and until the normal balance of carbonic acid and sodium bicarbonate is recovered, the subject breathes as if he were at a great altitude. Indeed, in this respect his condition approximates that of a man who has been taken to a great altitude in an aeroplane,[11] with forced acclimatization and coma as incidents of the trip. The blood alkali is abnormally low, but this condition is not, as we once thought, an acidosis. Alkali therapy is not indicated. The belief, common just now, that any condition in which the blood alkali is low is necessarily acidosis, is, as we have shown, incorrect.[12] It may be exactly the opposite condition.

With these facts before us, we can see what has not heretofore been realized, that the most acute period of tissue asphyxia, the time when the greatest injury is wrought to the nerve centers by the lack of oxygen, is the period of subnormal breathing after removal from the gas contained atmosphere. The conditions in the body are at first not appreciably better than before removal from the gassing chamber.

CARBON DIOXID AS A FACTOR IN TREATMENT

When, however, we added 8 to 10 per cent. carbon dioxid to the oxygen, an altogether different result was obtained.[8] Under inhalation of this mixture, the breathing is quickly restored to normal, or more than a normal amount. With the aid of this full ventilation of the lungs, the mass action of oxygen in the alveoli quickly displaces carbon monoxid from the blood. Certain other changes also occur in the blood, dependent on the restoration of its carbon dioxid, and the recall of alkali from the tissues. Thus, in ten or fifteen minutes

11. Henderson, Yandell: Science, 1919, pp. 431-441. Henderson, Yandell; Seibert, E. G.; Schneider, E. C.; Whitney, J. L.; Dunlap, Knight; Wilmer, W. H.; Berens, Conrad, Jr.; Lewis, E. R., and Paton, Stewart: Aviation, J. A. M. A. **71**: 1382-1400 (Oct. 26) 1918.

12. Haggard, H. W., and Henderson, Yandell: J. Biol. Chem. **39**: 163 (Aug.) 1919; **43**: 3 (Aug.) 1920.

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the subjects (dogs) are on their feet, virtually restored.

In this treatment, we believe that we have the long sought and ideal therapy for carbon monoxid poisoning. But its application will require a rather specialized apparatus. Such apparatus was devised by us for oxygen inhalation for gassed soldiers during the war, but it did not then come into extensive use. Oxygen containing 8 per cent. carbon dioxid is not yet on the market. Developments in these matters are under way. Throughout we have had the encouragement and assistance of the United States Bureau of Mines, without which we should not have reached the result described above. Few agencies in America do more for science and humanity than this great bureau.

For miners gassed after dust explosions, and for men overcome during rescue and salvage operations in mine fires, this treatment will, we are confident, considerably diminish suffering, and, let us hope, the number of fatalities also. It has an equally direct applicability to the treatment of city firemen overcome by smoke. Heretofore there has been little that medicine could do even to alleviate the headache and nausea of the gassed firemen. For these two classes of cases, the waiting ambulance and physician can provide immediate oxygen-carbon dioxid inhalations. Under such conditions, unless our experiments are much less significant than they now appear, this therapy should be effective.

ILLUMINATING GAS POISONING

It is not so probable that the ordinary overnight case of illuminating gas poisoning will be as easily helped. These are usually cases of prolonged asphyxia; and with the delays of discovery, calling police, telephoning for the ambulance, and getting to the hospital, time is lost which may be vital. The crucial feature of the proposed inhalational therapy is the termination of the tissue asphyxia at the earliest possible moment. After the harm is wrought, mere removal of carbon monoxid from the blood will not restore degenerated nerve cells.

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We can only hope that even in such cases the oxygen-carbon dioxid inhalation, by restoring carbon dioxid to the blood, recalling alkali from the tissues, and supplying oxygen, may arrest the degenerative processes.

However, on this aspect of the problem, experience alone can give a decisive answer and, until it is available, we must suspend judgment.

ABSTRACT OF DISCUSSION

DR. ROYD R. SAYERS, Washington, D. C.: The U. S. Bureau of Mines is especially interested in carbon monoxid poisoning and its treatment, owing to its frequent occurrence in the industries with which we are associated. In mines it occurs after fires, after explosions due to coal dust or gases, and after the use of explosives; and in smelters about the preroasters, roasters, blast furnaces, flues and bag houses. We also find it about petroleum refinieries. While I do not minimize the great danger of this gas, I do want to emphasize what seems to me an unwarranted amount of fear or hysteria regarding it. Dr. Henderson has called your attention to this. Both men and animals develop a partial tolerance to this gas after having been exposed to increasing amounts over a considerable period. Dogs have developed sufficient tolerance to have no bad effects after exposure for several hours to 0.8 per cent. Recently I have seen a partial tolerance in a canary bird which we were using in some experiments. This canary can stand fully twice the concentration of a bird not previously exposed. After exposure of two hours to 0.16 per cent., it was active and able to hop from its perch to the bottom of the cage and back again, while an analysis of my own blood, I having remained with the bird the entire time, showed the blood to be 47 per cent. saturated with the gas. Continuing these experiments on myself, I remained on other days in the gas sufficiently long to produce a saturation of from 36 to 40 per cent., after which, for the elimination of the carbon monoxid, breathing pure oxygen was compared with the breathing of a mixture of about 9 per cent. carbon dioxid, 89 per cent. oxygen, and 2 per cent. nitrogen. The oxygen-carbon dioxid mixture increased the lung ventilation from 300 to 400 per cent. over the normal. Oxygen (98 per cent.) produced no increased lung ventilation. The carbon monoxid was eliminated from the blood rather rapidly during the first ten or fifteen minutes with the use of either; but some carbon monoxid could be found in the blood for five or more hours later, but could not be detected after twenty-four hours. The mixture or the pure oxygen was breathed for forty-five minutes on each test. We are trying the two methods on dogs after sufficient

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exposure to cause profound unconsciousness, but this work is not completed. At the present stage of our experiments for the conscious man poisoned by carbon monoxid, the breathing of pure oxygen seems to give better results as to relief of symptoms and almost as rapid elimination of carbon monoxid from the blood as does the carbon dioxid-oxygen mixture.

DR. YANDELL HENDERSON, New Haven, Conn.: I can guarantee, from my own experience, that although we talk a little lightly about carbon monoxid, to get one's blood 47 per cent. saturated, as Dr. Sayers did, is an experience which one does not want to undertake lightly. It is heroic. It takes a man of great equilibrium and sweet temper to do it and still be tolerant toward the paper he is to discuss. With regard to the oxygen-carbon dioxid apparatus, it is virtually an oxygen inhaler somewhat like that used in the Bureau of Mines for gassed miners. It is important to be economical of oxygen, because you cannot carry a great many cubic feet. Once you stimulate respiration it uses up oxygen pretty fast. The apparatus is now being tested out at the Bureau of Mines Experiment Station in Pittsburgh. It was developed originally for the treatment of soldiers gassed with the irritant war gases in France, but the war came to an end before it came into use. A question has been asked me with regard to the lung motor, the pulmotor and other mechanical apparatus. The standpoint which seems to me to be justified now by eight years of experience, since the first commission investigated the matter, is that even if we had an ideally perfect apparatus for giving artificial respiration, it would still be better to discourage, and even to forbid the manufacture, sale, use and introduction of such apparatus, because it leads to delay, and thus to more deaths—deaths which could and should be restorations. If a man is drowned to the point at which he has stopped breathing, and his heart is beating only feebly, or if a man has gotten hold of a live wire and his respiration has stopped, you have often only two or three minutes within which life can be restored. Now, it is impossible for us all to go around with a lung motor or any other apparatus strapped to our backs all the time: hence an often fatal delay. Laboratory experience shows also that for most cases the manual method is actually better. Dr. Meltzer was strongly of the opinion, and I think he was justified, that mechanical apparatus very often injures the lungs seriously. On the other hand, the manual, or Schäfer method has a large number of clear cut recoveries to its credit. The supremely important point, as experience proves, is that you cannot have people prepared to give the manual method, and you cannot introduce routine training, if they know that when they telephone for a lung motor or pulmotor, it will come. I am more and more strongly of the opinion that the introduction of apparatus actually increases fatalities.

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THE PREVENTION OF SIMPLE GOITER IN MAN*

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Simple or endemic goiter is one of the most benign and insidious diseases of man and animals. The sum total of its ravages throughout all ages and in all lands is still unrealized by the public generally, notwithstanding the numerous reports of commissions appointed for its study. Those who live on the sea coasts fortunately have had no need to be concerned; and those who lived in goiter districts—before the days of extensive travel—grew accustomed to look on goiter as natural and normal. Indeed, in many districts of the world, it is still looked on as a mark of beauty.

Simple goiter includes all those thyroid enlargements in man and animals formerly grouped as endemic, epidemic, sporadic and physiologic. It must be sharply distinguished from exophthalmic goiter, with which it has no necessary association or etiologic relationship. Exophthalmic goiter, so far as it yet definitely known, occurs spontaneously only in man, while simple goiter occurs in all animals having the ductless thyroid. Exopthalmic goiter is not notably associated with districts, while with simple goiter this is most characteristic. Exophthalmic goiter occurs more frequently in the

* From the Laboratories of Western Reserve University, Cleveland, and Montefiore Hospital, New York.
* This investigation has been made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

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highly developed and civilized races, while in simple goiter race is not a factor. Simple goiter may develop sporadically in any place (even at sea, as reported on one of Captain Cook's voyages), but it is preeminently associated with certain regions or districts. The distribution of these districts of endemic goiter throughout the world was fully described by Hirsch, in 1860. The actual incidence of goiter within a given district is still quite unknown. With the information at present available, however, one can distinguish between mildly and severely goitrous districts. As compared with certain other districts, for example, the Alps and the Himalaya regions, our most important districts, namely, the Great Lakes Basin and the Cascade Mountain regions of Oregon, Washington and British Columbia, would be classified as mildly goitrous. The mildness or severity of a district may be determined by the incidence of myxedema or cretinism—a fact known to Morel and expressed in his famous dictum, "Goiter is the first halting place on the road to cretinism" (Le goître est la première étape sur le chemin qui conduit au cretinisme).

ETIOLOGY

The ultimate cause of simple goiter is totally unknown, notwithstanding a relatively large amount of study. The immediate cause is a lack of iodin. The enlargement, therefore, is a symptom and may result from any factor which increases the iodin needs of the organism, as in certain types of infection, or which interferes wtih the normal utilization of iodin; or it may result from actual experimental deprivation of iodin. The conception that it is due to a contagium vivum in the sense that this term is ordinarily used may be abandoned. Water has been associated as an etiologic factor by all peoples as far back as history goes. The American Indians (Barton) and the natives of Central Africa (Livingston) seem to have been as strongly convinced of the relation of water to the disease as was

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Hippocrates. If water is a factor, it would seem that it is the absence rather than the presence of some substance, which is to be considered, since goiter is associated with the purest of waters, chemically and bacteriologically as, for example, in Portland, Ore., and in Seattle and Tacoma, Wash., where there has been a rapid increase in goiter since these cities began to take their water supplies from the Cascade Mountains. After consideration of all the various substances, agents and theories that have been put forward as having a rôle in the etiology of goiter, we at present must fall back on the view that thyroid hyperplasia (goiter) is a compensatory reaction arising in the course of a metabolic disturbance and immediately depending on a relative or an absolute deficiency of iodin.

PATHOLOGIC ANATOMY

Anatomically, a wide range of changes may be present, depending on the species of animal and on the stage (duration) of the disease. It always begins with a decrease in the colloid material and a hypertrophy of the epithelial cells, at first cuboidal, later columnar, with infoldings and plications. In man and fowls, the stage most commonly observed is characterized by an abundance of colloid material—the so-called cystic or colloid goiter of the older writers—while in dogs, sheep, cattle, pigs, fish, etc., the accumulation of colloid is seen only in the late regressive or quiescent stages. In man, the adenomatous form (struma nodosa) is very common, but it is exceedingly rare in all the lower animals. These adenomas, in all probability, arise from fetal cell rests. The stimulus which initiates the growth of the cell rests (adenomas) and that which initiates the growth of the more differentiated thyroid tissue are probably identical. These growths have many of the attributes of tumor, in that their growth may not be arrested by iodin administration or by the natural physiologic compensation.

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EXPERIMENTAL PHYSIOLOGY

No accomplishment in preventive medicine has a firmer physiologic and chemical foundation than that underlying goiter prevention, and, as the work of prevention is based on certain of these facts, the more important may be reviewed.

1. The active principle of the thyroid is a very stable organic compound of iodin, first recognized by Baumann, in 1895, and recently (1916) isolated in crystalline form, by Kendall.

2. The developmental stage of all goiters is characterized by an increased blood flow, an increase in the size and number of epithelial cells, a decrease in the stainable colloid, and a marked absolute decrease in the iodin store. The decrease in the iodin store precedes the cellular hypertrophy and hyperplasia.

3. Similar changes (compensatory hyperplasia) invariably occur in the remaining portion of the gland, when a sufficient portion of the entire gland is removed. The amount of gland it is necessary to remove in order to cause compensatory hyperplasia varies somewhat with the species of animal, definitely, with the age, diet, and the presence or absence of iodin.

4. The administration of exceedingly small amounts of any salt of iodin in any manner completely protects the remaining thyroid against compensatory hyperplasia, even after the removal of three fourths of the normal gland in cats, dogs, rabbits, rats and fowls. Halsted and Hunnicutt reported a series of partial removals in dogs in which they failed to obtain compensatory hyperplasia, while Loeb has recently reported a series of partial removals in guinea-pigs in which iodin failed to prevent the compensatory hyperplasia, although desiccated thyroid still protected. He concluded that regeneration was physiologically different from spontaneous hyperplasia or simple goiter. The explanation for Halsted's results was probably that the

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animals were in contact with a source of iodin, while the most probable explanation for Loeb's results is that he removed too much thyroid, since, as shown by Marine and Lenhart, in 1909, iodin will not protect even in dogs if more than three fourths of the gland is removed, while desiccated thyroid will protect the animal against thyroid regeneration even after the removal of as much as nine tenths.

5. If most of the thyroid gland is removed before or in the early stages of pregnancy, and rigid precautions are taken to exclude iodin, the young at birth will have enlarged thyroids, as first shown by Halsted in dogs; while, if iodin is available, the young at birth will have normal thyroids.

6. A milligram of iodin, given at weekly intervals, has been found sufficient to prevent thyroid hyperplasia in pups.

7. Thyroid tissue has an extraordinary affinity for iodin, as has been demonstrated in vitro perfusions of surviving thyroids, and also by injecting intravenously small amounts of some soluble salt of iodin into the intact animal.

8. If the iodin store in the thyroid is maintained above 0.1 per cent., no hyperplastic changes, and therefore no goiter, can develop.

The foregoing experimental data seem to us sufficiently complete to demonstrate the underlying principles of goiter prevention, and the ease with which they may be applied. The first instance in which these facts were utilized in the prevention of goiter on a large scale occurred in 1909 and 1910. Working with endemic goiter in brook trout, Marine and Lenhart were able to demonstrate that iodin added to the water in a concentration not exceeding 1 : 1,000,000 arrested or prevented the development of thyroid hyperplasia (goiter). Since then, the method has been successfully applied on a large scale by several observers in the prevention of goiter in cattle, sheep, pigs and poultry.

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To our knowledge, the prevention of human goiter was not attempted on any large or practical scale until 1917, when we began work with the school population of the city of Akron, although in Cleveland it had been strongly urged and had been used by some physicians for several years. Briefly, the method as applied to man consisted in the administration of 2 gm. of sodium iodid in 0.2 gm. doses, distributed over a period of two weeks, and repeated each autumn and spring. This amount of iodin is excessive, and far beyond the needs of the individual or of the ability of the thyroid to utilize and store it. One gram distributed over a longer period would be better. The form or mode of administration of iodin is of little consequence. The important thing is that iodin for thyroid effects should be given in exceedingly small amounts, and it is believed that most of the untoward effects recorded are due to the excessive doses employed, or, more concretely, to the abuse of iodin. The results of our two and one half years' observations on schoolgirls in Akron are as follows: Of 2,190 pupils taking 2 gm. of sodium iodid twice yearly, only five have developed enlargement of the thyroid; while of 2,305 pupils not taking the prophylactic, 495 have developed thyroid enlargement. Of 1,182 pupils with thyroid enlargement at the first examination who took the prophylactic, 773 thyroids have decreased in size; while of 1,048 pupils with thyroid enlargement at the first examination who did not take the prophylactic, 145 thyroids have decreased in size. These figures demonstrate in a striking manner both the preventive and the curative effects. Klinger has recently (1921) reported even more striking curative results in the schoolchildren of the Zürich district. He worked with school populations in which the incidence of goiter varied from 82 to 95 per cent., while our maximum incidence in Akron was 56 per cent. With such a high natural incidence of goiter, his observations necessarily deal more with the curative effects. Thus

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of 760 children, 90 per cent. were goitrous at the first examination. After fifteen months' treatment with from 10 to 15 mg. of iodin weekly, only 28.3 per cent. were goitrous, of a total of 643 children reexamined.

The foregoing results were obtained in adolescents. There are two other periods in life when simple goiter frequently develops, namely, (1)) in fetal life and (2) during pregnancy. While the thyroid enlargements developing around the age of puberty are more common, they are not more important than those developing during pregnancy and fetal life. The higher birth mortality of infants with congenital goiter is well known. The thyroid enlargement of both mother and fetus may be prevented by giving 2 gm. of sodium iodid, or its equivalent in iodin in any other form, during the first half of pregnancy.

UNTOWARD EFFECTS

The dangers of giving iodin, in the amounts indicated, to children and adolescents are negligible. Exophthalmic goiter and iodism are the two important conditions to be looked for. No case of exophthalmic goiter developed in the series reported by Klinger or by us, although in both instances such cases were carefully looked for. Much has been written of iodin-exophthalmic goiters, but a study of the case reports reveals the fact that they resulted from the use of excessive (according to physiologic standards) amounts of iodin, or of desiccated thyroid. In adults, the possibility of aggravating a mild exophthalmic goiter or even the production of the syndrome in susceptible individuals must be considered. Again, the risk is slight. Iodin should not be given in any frank case of exophthalmic goiter unless the patient can be daily observed, and then it should be administered only in milligram doses. Iodism was observed in eleven cases among the schoolchildren of Akron during the two and one half years of observation. Most of these cases were very mild, and the girls

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did not stop the treatment. Klinger did not observe a single instance in sixteen months' observation on more than 1,000 children, although iodism was carefully looked for.

SUMMARY

Simple or endemic goiter in man may be prevented as cheaply and as simply as in the lower animals, by the administration of 3 to 5 mg. of iodin twice weekly, over a period of a month, and repeated twice yearly. Klinger in Switzerland has reported as striking, and nearly as extensive, results as those obtained by us in Akron. In young individuals, with goiter of recent development, the curative effects of exceedingly small amounts of iodin are as marked as one sees in goiter of animals. There are no dangers worthy of consideration associated with the administration of the quantities of iodin used by Klinger or by us. Simple or endemic goiter most commonly develops during (1) fetal life, (2) around the age of puberty, and (3) during pregnancy, and we believe that any plan which provides for its control during these three periods of life will practically eliminate endemic goiter. Goiter in the mother and fetus can be prevented as simply as that of adolescence, but, practically, it would seem that it is a responsibility of individual physicians, supplemented by public education. The prevention of goiter of childhood and adolescence should be a public health measure, best administered through the schools in order to combine the important additional factor of education. Beginning with the period of puberty, goiter occurs approximately six times as frequently in females as in males. The question, therefore, whether general prophylaxis should include both males and females would depend to some extent on whether the particular district was mildly or severely goitrous; hence the need for accurate surveys. The age of beginning and stopping the use of iodin would depend to some extent on race and climate. In the United States, probably the maximum

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of prevention coupled with the minimum of effort would be obtained by giving iodin between the ages of 11 and 17 years.

The prevention of goiter means vastly more than eliminating cervical deformities. It means, in addition, the prevention of those forms of physical and mental degeneration, such as cretinism, mutism and idiocy, which are dependent on thyroid insufficiency. Further, it would prevent the development of thyroid adenomas, which are an integral and essential part of endemic goiter in man, and due to the same stimulus. These multiple, circumscribed benign growths have many of the attributes of tumor, one of which is that their growth once initiated is frequently not controlled by iodin, as are all simple hyperplasias. The terminal metamorphoses are far more serious than those of simple hyperplasia, since, in addition to hemorrhage, necroses, cyst formation, etc., probably 90 per cent. of the malignant tumors of the thyroid arise from these adenomas.

If the prevention of goiter is good preventive medicine, it is better preventive surgery. With so simple, so rational and so cheap a means of prevention at our command, this human scourge, which has taken its toll in misery, suffering and death throughout all ages, can and should be controlled, if not eliminated.

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THERAPEUTIC VALUE OF CHAULMOOGRA OIL AND ITS DERIVATIVES IN EXPERIMENTAL TUBERCULOSIS

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AND

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Numerous attempts have been made in the past to discover chemicals which will cause the death of the tubercle bacillus within the body of infected animals. Soon after the discovery of this bacillus, Robert Koch himself tried to find drugs which might be useful in combating this disease. It is not our purpose in this paper to review the large amount of work done along this line. Suffice it to say that all of these attempts have been complete failures, notwithstanding the positive claims which were made from time to time. As a matter of fact, the specific treatment of diseases of bacterial origin has so far not yielded results comparable to those obtained in the treatment of diseases due to protozoa. The chemotherapy of bacterial diseases is, however, not a hopeless problem, as shown by the promising results obtained by Morgenroth and his colleagues with ethylhydrocuprein in the treatment of pneumococcus infection in mice, and the recent reports on the favorable action of chaulmoogra oil in leprosy.

The success reported in leprosy led us to test out the therapeutic value of chaulmoogra oil and its principal components in experimental tuberculosis, for the fol-

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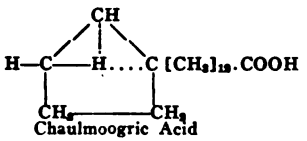
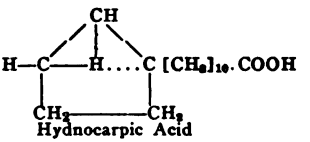
lowing reasons: (1) The leprosy and tubercle bacillus belong to the group of acid-fast bacteria, and (2) the work of Walker and Sweeney [1] seems to indicate that chaulmoogric acid, the specific acid contained in chaulmoogra oil, exerts a powerful action on all acid-fast bacteria, but is inert toward nonacid-fast organisms. Indeed, these authors present figures which show that chaulmoogric acid is 100 times more bactericidal than phenol for acid-fast bacteria, including the tubercle bacillus.

The chemistry of chaulmoogra oil has been worked out pretty thoroughly by the splendid researches of Power and his collaborators,[2] the results of which were confirmed and somewhat extended by Dean and Wrenshall [3] in a recent paper. According to this work the oil contains a large amount of chaulmoogric acid and hydnocarpic acid, which appear to possess the following constitution:



Chaulmoogric Acid



Hydnocarpic Acid

Both acids are optically active and differ from the ordinary fatty acids in containing a five-atom carbon ring with an unstable hydrogen atom. The acids can be readily converted into the ethyl esters, which seem to possess certain therapeutic advantages over chaulmoogra oil.

The guinea-pig was selected as the experimental animal on account of its great susceptibility to infection with tuberculosis, and the regular course and invariably fatal outcome of the disease when a proper dose of tubercle bacilli is used.

1. Walker, E. L., and Sweeney, M. A.: The Chemotherapeutics of the Chaulmoogric Acid Series and Other Fatty Acids in Leprosy and Tuberculosis, J. Infect. Dis. **26**: 238 (March) 1920.

2. Power, F. B., and Gornall, F. H.: J. Chem. Soc. **85**: 851, 1904. Power, F. B., and Barrowcliff, M.: Ibid. **91**: 557, 1907.

3. Dean, A. L., and Wrenshall, Richard: Fractionation of Chaulmoogra Oil, J. Am. Chem. Soc. **42**: 2626-2645, 1920.

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TOXICITY

As a preliminary to the therapeutic experiments, the toxic action of the compounds was studied on normal guinea-pigs. Chaulmoogra oil dissolved in olive oil or given as such intramuscularly is intensely irritating, and leads to local swelling and necrosis of the tissues even in small doses (1 c.c.). On microscopic examination, the site of injection shows atrophy and fatty degeneration of the muscle fibers, this change occurring at times with doses as small as 10 mg. Subcutaneous administration of the oil gives rise to local hemorrhages, thickening and necrosis. The ethyl ester of chaulmoogric acid is somewhat less objectionable in this respect, but even this compound causes some local irritation and microscopic changes. Intraperitoneal injection of the ethyl ester seems to be tolerated in fairly large amounts. After repeated injections, the peritoneal cavity on necropsy is found to contain a large amount of precipitated material covering the spleen and liver which appears to be fibrin. Adhesions are nearly always present, especially in the tuberculous animals treated with this substance. The sodium salt of chaulmoogric acid in 2 per cent. aqueous solution can be injected intravenously at a slow rate without causing any evident symptoms. If the rate is too rapid, however, the animal dies of what appears to be embolism, as under these conditions the free acid seems to be precipitated in the blood stream. Furthermore, the solution of the sodium salt is strongly alkaline, and has therefore a destructive effect on the vein used for the injection, so that each vein can be used only once. On account of this difficulty, the use of the sodium salt had to be abandoned. We conclude from our toxicity experiments that chaulmoogra oil and chaulmoogric acid and its derivatives are substances of relatively tow toxicity, but possessing irritating properties which make their therapeutic administration somewhat difficult, a fact which is also borne out by the clinical reports on their use in leprosy.

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TREATMENT

Guinea-pigs weighing from 200 to 250 gm. were kept for a preliminary period of observation in well-constructed cages, and were fed on oats, cabbage and carrots. The growth curve of the animals was determined, and individuals showing no proper increase in weight were eliminated. We believe this to be an important measure which should be observed in all work of this type, as the reliability of the results is dependent on taking this precaution.

The material used for intraperitoneal inoculation consisted of a culture of a fairly virulent human strain of tubercle bacilli (H_{37}) which had been cultivated in this laboratory for several years on glycerin broth. In the three series of experiments here reported, fifteen, forty-nine and thirty controls, respectively, were inoculated with the same emulsion as the animals which were subjected to treatment. In the first series the dose was 0.001 mg., and for the second and third series 1 mg. of a culture five to six weeks old. The animals were weighed once a week. A careful necropsy was made in nearly all cases, and the findings were confirmed by histologic examinations of the lesions.

The chaulmoogra oil used was obtained from India and conformed with the the requirements of the British Pharmacopeia. The chaulmoogric acid was prepared in chemically pure form. The ethyl ester was obtained from a mixture of chaulmoogric and hydnocarpic acids and was purified by vacuum distillation. Part of the ester was converted into a saturated compound by adding 5 gm. of the ester to 1.92 gm. of iodin dissolved in 5 gm. of absolute alcohol. This compound is referred to as the iodin saturated ethylchaulmoograte.

SERIES I.—Inoculated with 0.001 mg. of tubercle bacilli emulsion.

Group 1. Fifteen controls.

Group 2. Thirty-six animals. Each received 80 mg. per kilogram of sodium chaulmoograte (2 per cent. solution) intravenously about every ten days. Total dose of chaulmoogric

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acid: maximum, 240 mg. per kilogram; minimum, 100 mg. per kilogram.

Group 3. Thirty-four animals. Each received 80 mg. per kilogram of sodium chaulmoograte (2 per cent. solution) intravenously about every ten days, and 100 mg. per kilogram of calcium lactate (2 per cent. solution) intravenously as a separate injection every ten days. Total dose of chaulmoogric acid: maximum, 160 mg. per kilogram; minimum, 80 mg. per kilogram. Total dose of calcium lactate: maximum, 200 mg. per kilogram; minimum, 100 mg. per kilogram.

SERIES II (Chart 1).—Inoculated with 1 mg. of tubercle bacillus emulsion.

Group 1. Forty-nine controls.

Group 2. Fifty animals. Each received 75 mg. of ethylchaulmoograte in olive oil (25 per cent. solution) intraperitoneally three times a week.

Group 3. Fifty animals. Each received 250 mg. of ethylchaulmoograte in olive oil (50 per cent. solution) intraperitoneally three times a week. Total dose of last two groups: maximum, 15 c.c.; minimum, 4.5 c.c. of ester.

SERIES III (Chart 2).—Inoculated with 1 mg. of tubercle bacillus emulsion.

Group 1. Thirty controls.

Group 2. Thirty animals. Each received 10 to 20 mg. chaulmoogra oil[4] intramuscularly once a week.

Group 3. Thirty animals. Each received 10 mg. of ethyl ester intramuscularly once a week.

Group 4. Thirty animals. Each received 10 mg. of iodin saturated ethylchaulmoograte intramuscularly once a week.

Group 5. Twenty-nine animals. Each received 100 mg. of undiluted ethyl ester plus 10 mg. of sodium iodid intramuscularly once a week.

Group 6. Thirty animals. Each received from three to forty-six injections of from 10 to 250 mg. each of the ethyl ester intramuscularly or intraperitoneally for several weeks prior to infection and same treatment continued until death.

RESULTS

In the search of remedial agents for the treatment of tuberculosis, it can scarcely be hoped to find a substance which would save all or even a certain number of infected animals from death, as tuberculosis in the guinea-pig is a more acute disease and the natural resistance is much lower than in man. A full appreciation of this point of view led us to adopt the following

4. The chaulmoogra oil, ethyl ester and iodin compound were given in 5 per cent. emulsion in water, containing 20 per cent. alcohol.

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criteria as evidence of therapeutic action: (1) the effect of treatment on the mortality curve; (2) the extent and character of the tuberculous process at the end of the experiment, and (3) the influence of treatment on the body weight. The study of the effect of the treatment on the mortality curve obviously necessitates working with a large number of animals. This is rarely done by workers in this field, probably on account of the large amount of work and considerable expense involved. Nevertheless, it appeared to us of great importance to carry out our work on a large scale in order to eliminate differences in individual resistance to the infection and differences in the behavior of the body to the drug, factors which undoubtedly are of great importance in the proper estimation of the value of drugs. The character of the pathologic changes at necropsy is generally recognized as a valuable index of the defensive power of the body against infection. Careful attention was, therefore, paid to the extent and character of the lesions. Changes in the growth curve of young animals as influenced by the disease and the treatment are also of unquestionable importance. A typical growth curve is given in Chart 3, and this shows that almost the normal rate of growth is maintained for a considerable length of time; later on a gradual decline sets in, which just prior to death becomes precipitous. In some animals the body weight changes very little for several weeks, until the resistance to infection gives way and the animal declines.[5] The advantage of using growing guinea-pigs is therefore obvious.

In Series I, some of the animals died in the course of some weeks with evidence of tuberculosis. The remainder of the animals were chloroformed sixty-five days after the inoculation. The animals of this series had received a very small dose of tubercle bacilli, only 0.001 mg., and the infection was evidently a very mild

5. De Witt, Lydia M.: Weight Curves of Tuberculous Guinea-Pigs, J. Infect. Dis. 27: 503-512 (Nov.) 1920.

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one, as shown by the fact that only 27 per cent. of the control animals had definite tuberculous lesions. In the group which was treated with sodium chaulmoograte, 72 per cent. showed evidence of tuberculosis, and in that with chaulmoograte and calcium lactate, 62 per cent. The calcium lactate was used with the idea that it might favor calcification. The conclusion seems therefore justified that the tuberculous process was not inhibited by the treatment in spite of a very mild type of infection.

TABLE 1.—WEIGHT CHANGES AND AVERAGE LENGTH OF LIFE IN SERIES II

	Group 1 (Controls)	Group 2	Group 3
Average number of weeks of maintained weight	9.4	7.6	7.0
Average number of weeks of ascending part of growth curve	6.8	5.1	5.1
Average of weeks of descending part of growth curve	3.0	3.0	3.1
Average length of life in days	105.9	94.2	82.0

TABLE 2.—EXTENT AND CHARACTER OF LESIONS FOUND AT NECROPSY IN SERIES II

	Group 1 (Controls)	Group 2	Group 3
Percentage of animals showing:			
No lesions	..	..	2 (21st day)
Localized	4	..	6
Moderate generalization	35	41	37
Generalization with caseous necrosis	61	59	55

TABLE 3.—EXTENT OF LESIONS OBSERVED AT NECROPSY IN SERIES III

	Group 1 (Controls)	Group 2	Group 3	Group 4	Group 5	Group 6
Average length of life in days	54	47	50	58	56	59
Percentage of animals showing:						
No lesions	..	..	..	6	..	..
Localized lesions	..	..	3	7	..	3
Moderate generalization	40	50	43	57	32	43
Generalization with caseous necrosis	60	50	54	30	68	54

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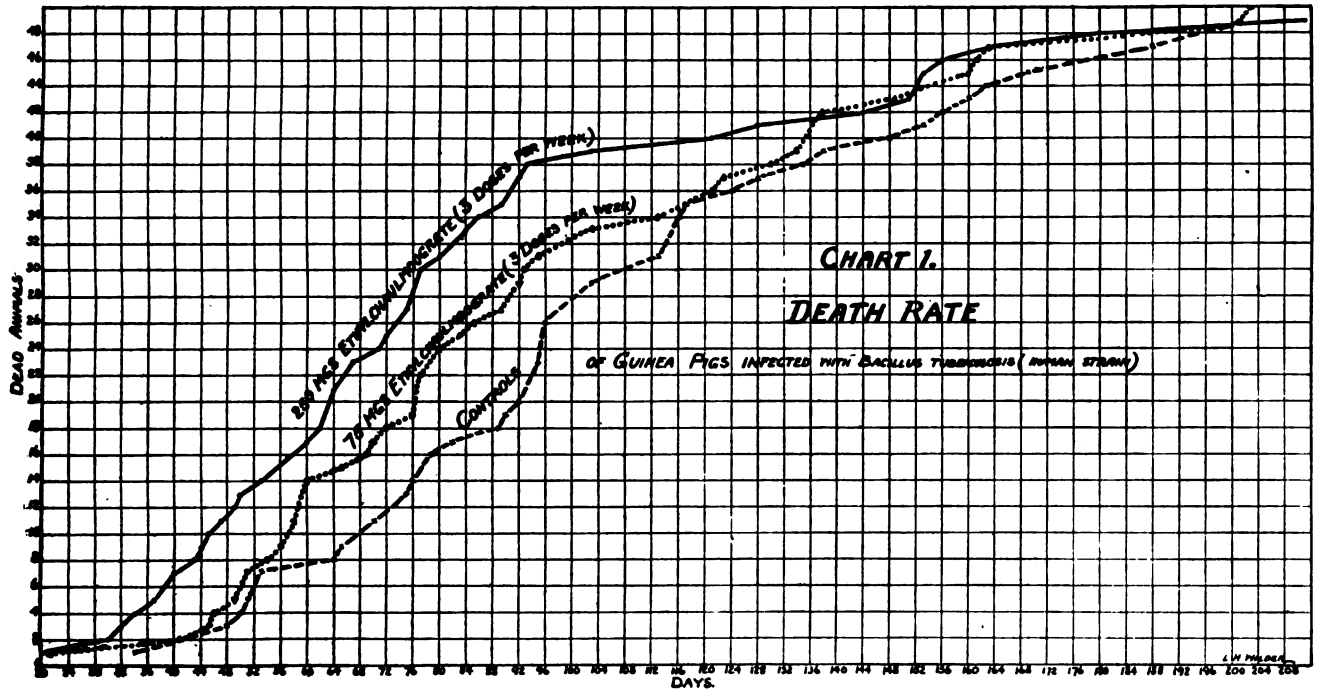

Chart 1.—Death rate of guinea-pigs infected with Bacillus tuberculosis (human strain).

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In Series II the infection was of a more virulent nature than in Series I. Table 1 summarizes the weight changes and the average length of life of the animals of the three groups. Table 2 contains the data relating to the extent and character of the lesions found at necropsy, and Chart I the mortality curves. It will be

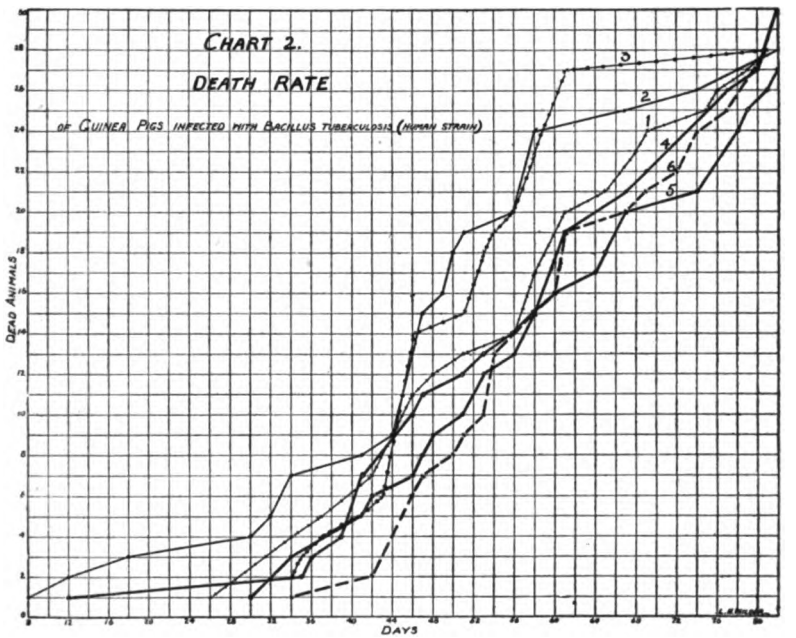

Chart 2.—Death rate of guinea-pigs infected with Bacillus tuberculosis (human strain).

seen that the treatment had no favorable action whatsoever. The mortality curves of the treated animals are somewhat more steep, which may possibly indicate that the treatment had a deleterious effect.

In Series III the animals showed a still more acute type of the disease, as is illustrated by Chart 2. The treatment had no effect on the morality rate, growth curve and extent of the lesions observed at necropsy (Table 3).

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The iodin preparation was used on account of the work of Jobling and Petersen,[6] who showed that iodin has an inhibiting effect on the antiproteolytic ferments of the blood. It was thought that the iodin through indirect action might render the tubercle bacilli within the lesions more accessible to the drug. Emphasis should be placed on the fact that the animals in Group 6 were treated with ethyl esters before and after infection. Even this intensive treatment had no effect on the course of the disease.

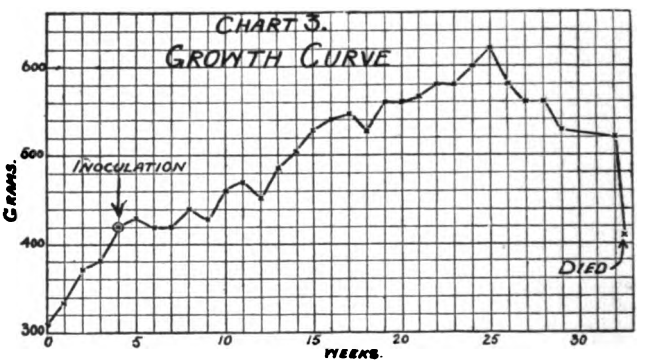

Chart 3.—Growth curve.

The net result of this exhaustive experimental test of the value of chaulmoogra oil and its derivatives is therefore negative. After the completion of this work a paper appeared by Kolmer, Davis and Jager [7] reporting some experiments with chaulmoogra oil in the treatment of guinea-pigs infected with a bovine strain. Only six animals were treated, and the results were entirely negative.

6. Jobling, J. W., and Petersen, William: The Therapeutic Action of Iodin, Arch. Int. Med. **15**: 286-302 (Feb.) 1915.

7. Kolmer, Davis and Jager: Chaulmoogra Oil in Tuberculosis. J. Infect. Dis. **28**: 265 (March) 1921.

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TREATMENT OF ARTHRITIS

CHEMICAL AND CLINICAL STUDIES WITH THE SALICYLATES, AND CINCHOPEN AND NEOCINCHOPHEN *

ARTHUR F. CHACE, M.D.

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AND

JOHN A. KILLIAN, PH.D.

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In 1875, Büss [1] used sodium salicylate in the treatment of rheumatic fever, and since that time salicylates have been regarded as almost specific in the treatment of acute infectious arthritis. Cinchophen was introduced as a remedy for gouty arthritis, owing chiefly to the discovery of its strong uric acid eliminating powers. It has been recognized since the observations of Garrod,[2] more than seventy years ago, that infectious arthritis, differing from gouty arthritis, is not associated with retention and deposition of uric acid; still there has been a tendency among many physicians to regard infectious arthritis as associated with a disturbed uric acid elimination. Although high figures for the uric acid of the blood (from 5 to 10 mg. per hundred cubic centimeters) are almost invariably found in untreated cases of gout, cases of nongouty arthritis seldom show abnormal findings for this blood constituent, except an occasional case with renal complications. Although, as

* From the Department of Medicine and the Laboratory of Pathological Chemistry, New York Post-Graduate Medical School and Hospital.

1. Büss, C. E., cited by Hanzlik, P. J.: The Salicylates: I, A Historical and Critical Review of the Literature, 1914, Annual Report of the Therapeutic Research Committee of the Council on Pharmacy and Chemistry of the American Medical Association.

2. Garrod, A. B.: Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism and Bright's Disease, Med.-Chir. Tr. 21: 83, 1848.

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already pointed out, the salicylates have been employed in infectious arthritis largely because of their analgesic and antipyretic properties, and cinchophen has been employed in gout because it stimulates uric acid excretion, a closer study of these two classes of compounds has shown that, in general, they possess somewhat the same properties, i. e., the salicylates also increase the elimination of uric acid, and cinchophen possesses analgesic properties. It is a singular fact that drugs possessing such similar therapeutic properties should have come, for entirely different reasons, to be used in the treatment of infectious and gouty arthritis. This has led us to believe that, after all, these two forms of arthritis may possibly possess something in common.

EFFECTS OF SALICYLATE THERAPY

We have again [3] undertaken a study of the blood uric acid, together with the urea and creatinin, of nongouty arthritics before and during the period of drug therapy, with the hope that such observations might add to our knowledge of this subject. In a comparatively recent paper, Denis [4] has made the suggestion, in connection with the increased uric acid elimination following the administration of salicylates, that the beneficial effects resulting from their use in acute rheumatic fever "may in part at least be due to a power possessed by this class of drugs of increasing kidney permeability, thereby facilitating the rapid and more or less complete excretion of the as yet unknown toxins which produce symptoms of this disease." If this hypothesis should be correct, one would expect a fairly definite relationship between the therapeutic efficacy and the decrease in the uric acid content of the blood. From a study of our actual observations (summarized in the accompanying

3. Chace, A. F., and Fine, M. S.: The Use of Atophan and Radium Emanation in the Treatment of Gout and the Arthritides, J. A. M. A. **63**: 945 (Sept. 12) 1914.

4. Denis, W.: J. Pharmacol. & Exper. Therap. **7**: 255 (Oct.) 1915.

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table), there appears to be very little relation between the drop in the blood uric acid and the clinical improvement.

In connection with this work, however, we have made the interesting observation, the details of which are being reported elsewhere,[5] that the administration of these drugs may reduce the blood concentration not only of uric acid, but also of urea and chlorids, particularly in cases in which there is slight retention of these substances. Although the excretion of uric acid is apparently stimulated considerably more than that of any of the other urinary constituents, still it is obvious that these drugs are much more than simply "uric acid eliminants." Most of our studies in this connection have been made with neocinchophen and cinchophen, although the salicylates probably produce similar effects. It is of interest that, whereas moderate doses of these drugs stimulate the function of the kidney, Hanzlik, Scott and Thoburn [6] have pointed out that full therapeutic doses of the salicylates given to the point of toxicity produce the opposite effect.

The influence of these drugs on the composition of the blood has been studied in a series of more than fifty cases, in about one fourth of which the patients were suffering from arthritis. Tabular data are given for eleven of the arthritis cases. The analytic methods employed for the blood analyses were carried out as already described.[7] Our clinical deductions are based partly on the observations in these cases and partly on observations in a large series of cases in the private practice of one of us (A. F. C.).

5. Myers, V. C., and Killian, J. A: Studies on the Influence of Phenylcinchoninic Acid and the Ethyl Ester of Paramethylphenylcinchoninic Acid on Renal Excretion, J Pharmacol. & Exper. Therap., to be published.

6. Hanzlik, P. J.; Scott, R. W. and Thoburn, T. W.: The Salicylates: -VII, Further Observations on Albuminuria and Renal Functional Changes Following the Administration of Full Therapeutic Doses of Salicylates, Arch. Int. Med. **19**: 1029 (June) 1917.

7. Myers, V. C.: Practical Chemical Analysis of Blood, St. Louis. C. V. Mosby Company, 1921.

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INFLUENCE OF SODIUM SALICYLATE, CINCHOPHEN AND NEOCINCHOPHEN ON THE URIC ACID OF THE BLOOD IN INFECTIOUS ARTHRITIS

Case and Diagnosis	Date, 1920–1921	Blood Analyses Mg. to 100 C.c. Uric Acid	Urea N	Creatinin	Medication
1. R. H., man, aged 31, acute infectious arthritis	4/30	Trace	17.2	2.3	Salicylates previous to admission; neocinchophen, 50 grains daily, 5/1-7
	5/ 1	2.0	14.4	1.8	
	5/ 7*	1.8	14.2	1.6	
	5/ 9	2.1	10.5	1.4	
2. L. G., man, aged 42, acute infectious arthritis	1/ 5	2.7	10.0	2.1	Sodium salicylate given, 240 gains daily by rectum in 1 per cent. starch solution, 1/6-9
	1/ 6	2.6	10.3	1.9	
	1/ 9*	2.7	15.2	2.5	
	1/10	3.0	16.0	2.3	
	1/13	2.9	14.9	2.5	
3. N. T., man, aged 30, acute infectious arthritis, endocarditis	1/ 6	2.2	14.7	2.2	Neocinchophen, 100 grains daily, 1/7-11
	1/10*	1.0	10.0	2.0	
	1/12*	0.0	9.7	2.0	
	1/15	2.7	12.3	2.1	
4. S. F., woman, aged 43, acute infectious arthritis	11/24	3.0	11.8	1.8	Sodium salicylate, 180 grains daily with sodium bicarbonate, 11/25-27; neocinchophen, 45 grains daily, 12/2, 75 grains, 12/3, 100 grains, 12/4-5, 180 grains, 12/8, and 200 grains, 12/9-18
	11/28*	Trace	12.0	1.9	
	12/ 1	1.4	11.0	...	
	12/ 5*	Trace	8.7	1.8	
	12/ 7	2.7	11.5	2.0	
	12/16*	1.2	12.2	2.0	
	12/18*	1.7	12.1	2.1	
5. H. J., man, aged 34, acute infectious arthritis	4/17*	1.3	14.2	...	Sodium salicylate and sodium bicarbonate, 120 grains each daily, 4/9-16; neocinchophen, 50 grains daily, 4/22-24; cinchophen, 50 grains daily, 4/30-5/1
	4/20	1.7	16.2	1.9	
	4/22	2.2	15.0	1.8	
	4/26*	1.8	13.6	...	
	4/30	2.0	17.2	1.4	
	5/ 1*	1.5	17.1	1.8	
	5/ 7	2.2	18.0	2.0	
6. G. F., man, aged 20, acute infectious arthritis	5/ 1	2.3	10.0	1.5	Neocinchophen, 50 grains daily, 5/2-7
	5/ 2	2.2	10.2	1.4	
	5/ 7*	1.8	10.8	1.6	
	5/ 9	2.6	11.7	1.5	
7. C. R., woman, aged 47, acute infectious arthritis	4/20	2.6	15.7	2.1	Neocinchophen, 50 grains daily, 4/20-22 and 24-27
	4/28*	2.5	13.9	2.2	
8. G. E., man, aged 44, acute infectious arthritis	4/30	3.6	16.3	1.8	Neocinchophen, 50 grains daily, 5/1-8, and cinchophen, 50 grains daily, 5/11-15
	5/ 1	3.6	15.1	1.5	
	5/ 6*	3.1	15.4	2.0	
	5/11	3.6	18.0	2.3	
9. J. McG., man, aged 40, chronic arthritis	11/ 5	4.5	18.2	2.0	Purin-free diet, 11/11-15; cinchophen, 50 grains daily, 11/18-21; neocinchophen, 50 grains daily, 11/27-30, 75 grains, 12/1, 100 grains, 12/2
	11/11	3.3	....	...	
	11/15	2.5	12.4	...	
	11/22*	2.0	....	1.9	
	11/27	2.0	13.2	1.9	
	11/30*	1.5	12.6	...	
	12/ 2*	3.5	11.2	2.0	
	12/ 3*	2.4	11.2	2.2	
10. A. P., woman, aged 60, chronic arthritis, with renal impairment	9/20	5.9	21.9	1.9	Low protein diet; cinchophen, 37.5 grains daily, 9/30-10/9
	9/29	5.6	22.9	2.0	
	10/ 3*	2.0	21.7	...	
	10/ 6*	2.5	17.2	...	
	10/10*	Trace	18.7	2.1	
11. E. R., woman, aged 38, chronic arthritis	3/ 7	2.6	10.6	2.2	Neocinchophen, 50 grains daily, 3/10-12, and 100 grains daily, 3/16-18
	3/10	2.9	10.9	2.2	
	3/13*	2.8	11.6	2.5	
	3/16	3.4	10.5	1.9	
	3/19*	1.4	11.1	1.5	

* Blood analyses after medication.

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A few pertinent clinical facts regarding the individual cases are here presented:

REPORT OF CASES

CASE 1.—A man gave a history of pain and swelling in the joints for five weeks previously; salicylates had been given before admission, without improvement. The patient was brought in by stretcher. After the first day of neocinchophen therapy, the temperature dropped from 101 F to 99 F. and remained normal thereafter. At the end of two weeks, the patient was sleeping well, and did not complain of pain. He left the hospital, recovered.

CASE 2.—A man was admitted by ambulance, complaining of severe pains in the joints and swelling of the forearms. He was unable to use the arms. His temperature was 103 F.; leukocytosis 15,400, polymorphonuclears 83 per cent. Following four days of salicylate therapy by rectum, the patient was fairly comfortable, and slept at intervals. Three days later he was greatly improved, was out of bed, and able to use both arms; so he left the hospital. At all times, the urine contained a small amount of protein, and red and white blood cells.

CASE 3.—A man was admitted by ambulance, complaining of severe pains in the forearms. He was unable to use the arms. Examination revealed a temperature of 103 F.; leukocytes 17,100, with polymorphonuclears 83 per cent.; urine protein + +. Neocinchophen was administered by mouth, 100 grains daily for five days. After two days of this therapy, the urine protein was +, and at the end of the period, negative. After two days the patient was free from pain; after six days he could use his arms freely, and was out of bed; ten days after admission, he left the hospital, cured.

CASE 4.—A woman, on admission, complained of extreme pain in right leg and arm, and swelling and stiffness in both limbs. Her temperature was 100-101 F. She was at once put on sodium salicylate and sodium bicarbonate. From admission, she was restless and unable to sleep, and on third night delirious. The salicylates were discontinued. On admission, the urine protein was negative, but before the salicylates were discontinued it was + + + +, with many red cells and a moderate number of leukocytes in the sediment. After a three days' interval, neocinchophen administration was started, and was raised gradually to 200 grains daily. After discontinuance of the salicylates, the urine protein dropped to +, and was uninfluenced by the neocinchophen. The patient considerably improved the first day of neocinchophen therapy, and markedly improved on the third day. No deleterious effects were noted from the rather large doses. The patient recovered.

CASE 5.—A man was admitted by stretcher, helpless and complaining of severe pain in arms, legs and back. The onset occurred five weeks previously. Examination revealed

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leukocytes, 18,000, and temperature 103 F. At once sodium salicylate and sodium bicarbonate were given by mouth, with local applications of methyl salicylate. After one week, the treatment was discontinued. The pains were still severe, and temperature was 102 F. After a five-day interval, during which the patient did not improve, neocinchophen was started. The next day he was free from pain, and could use the arms very well. The fourth day, he was out on the roof, felt very well and had no pains. Recovery ensued.

CASE 6.—A man was admitted complaining of swelling and pain in both hands and the right foot, of twelve hours' duration. Examination revealed a temperature of 103 F.; leukocytes 18,000, with 83 per cent. polymorphonuclears. Neocinchophen therapy was instituted; and after six days, the swelling of the hands and feet was reduced, and the pain coincident with movement of the joints was markedly reduced. Next day the patient was in a chair, feeling greatly improved. Recovery followed.

CASE 7.—On admission, a woman complained of severe pains in both arms and hands, and of stiff joints. She was unable to sleep. The leukocyte count was 23,200; the temperature before therapy 102-102.4 F. At the end of the first day of neocinchophen therapy, the patient was fairly comfortable. The urine was negative. At the end of ten days, she was sleeping very well and complained of no pain. Recovery followed.

CASE 8.—A man suffered from severe pains in the arms and legs. There was a temperature of 101 F.; leukocytes numbered 16,600, and the urine showed a trace of protein and an occasional hyalin cast throughout his stay in the hospital. Neocinchophen was given for the first week, with considerable clinical improvement. It was discontinued for two days, whereupon severe pains reappeared. Cinchophen was then given for five days, with marked improvement. The patient was discharged, improved.

CASE 9.—There had been swelling and pain in the knee joints, shoulder joints, wrists and elbows for five years previously. There was no rise in temperature, nor leukocytosis. The patient was improved by dietary measures, but after four days of cinchophen therapy he was able to be up in a wheel chair; after a six-day interval, neocinchophen therapy was begun. The knee joints, which had especially troubled the patient, were free from pain in four days, and he was able to walk about the ward with ease. The urine was negative throughout. The patient left the hospital markedly improved, except for deformity in the legs.

CASE 10.—A woman had chronic arthritis affecting both knees, and a tumor in left breast, probably malignant. There was no rise in temperature. Slight nitrogen retention was noted, but no proteinuria at any time. Cinchophen therapy

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was employed and caused nausea. The uric acid and urea of blood were appreciably reduced, but there was no marked clinical improvement. The patient was removed against advice.

CASE 11.—A woman complained of pains, with moderate degree of ankylosis in various joints, of ten years' duration. There was no rise in temperature, and the urine was negative throughout. Low carbohydrate diet was prescribed, with neocinchophen therapy after a short control period. The pain was relieved, but ankylosis remained unchanged. The patient left the hospital slightly improved.

COMMENT

Judging from our present studies, the excretion of uric acid is not so readily stimulated by these drugs in cases of infectious arthritis as in most other conditions. The relative inertness here noted is accentuated in advanced nephritis, in which these drugs may have little or no influence on the uric acid excretion.[8] In three of our eleven tabulated cases (3, 4 and 10), however, the blood uric acid was reduced to a trace, and in these cases there was also a noticeable drop in the urea. The absence of chemical blood changes in the remaining cases can probably be ascribed, in part at least, to the acquisition of a tolerance for this group of drugs.

As there appears to be no relation between the blood changes and the therapeutic efficiency of the different drugs, it seems improbable that the clinical improvement is in any way dependent on the increased excretion of uric acid or other substances by the kidney. We have been led to believe, as a result of unpublished experiments carried out in this institution by Simpson and Meeker, that the improved kidney function is probably dependent on an altered circulation in the glomeruli. Similarly, Dr. Hanzlik [9] has suggested that the benefit to the joints may possibly be attributed to local circulatory effects, which facilitate the interchange of inflammatory and metabolic products.

8. Fine, M. S., and Chace, A. F.: The Diminished Power of the Nephritic Kidney for Eliminating Uric Acid, Arch. Int. Med. **16**: 536 (Sept.) 1915.

9. Personal communication to the authors.

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Although our studies were begun with the idea of comparing the action of cinchophen [10] and sodium salicylate, many more observations have recently been made with neocinchophen than with cinchophen, for the reason that neocinchophen is much less liable to produce gastro-intestinal disturbances. Neocinchophen is an ester which appears to be quite inert in the stomach. We originally supposed that the therapeutic effects of neocinchophen would be less pronounced than those of cinchophen, but this idea does not appear to be borne out by our results.

In the doses which we employed, neither cinchophen nor neocinchophen produced proteinuria or intensified it when already present.

Cinchophen and neocinchophen, particularly the latter, appear to be very promising agents in the treatment of acute infectious arthritis. Drs. Hanzlik and Scott [9] write us that they have formed a similar opinion.

CONCLUSIONS

1. It may be stated in general that the salicylate and cinchophen groups of drugs show comparatively little difference in their analgesic, antipyretic and "uric acid eliminating" effects. It should be noted, however, that this latter term is not sufficiently inclusive, since these drugs also stimulate, to a lesser degree, the elimination of other waste products.

2. There appears to be no relation between the therapeutic efficiency of these drugs in infectious arthritis and their influence on the blood uric acid, a statement which is not generally regarded as applying to gouty arthritis.

3. In the series of cases here reported, cinchophen and neocinchophen seemed to have a more specific effect in the severe cases of infectious arthritis.

10. Cinchophen and neocinchophen are the terms adopted by the Council on Pharmacy and Chemistry of th eAmerican Medical Association to apply to phenylcinchoninic acid and the ethyl ester of paramethylphenylcinchoninic acid. The latter substance may now be obtained under the trade name of tolysin.

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4. The salicylates have the distinct disadvantage of producing marked proteinuria and casts when given in large doses. On this account, cinchophen and neocinchophen are the drugs of choice when, for any reason, it seems desirable to favor the kidneys. Furthermore, the latter drugs appear to produce their therapeutic effect through smaller doses.

5. The salicylates have the advantage of being better assimilated by rectum.

6. Cinchophen and neocinchophen, particularly when given with alkalis, are better tolerated by the stomach than salicylates. Since neocinchophen is an ester instead of an acid, there is less need of using alkali than with cinchophen. In fact, when given without alkali, neocinchophen does not seem to irritate the stomach.

7. Although a few cases of marked idiosyncrasy to the salicylates (acetylsalicylic acid), in the nature of an allergic reaction, have been reported, our experience is that patients are more liable to have vasomotor disturbances of the urticarial type from cinchophen. No serious instances of the latter have been observed.

525 Park Avenue.

ABSTRACT OF DISCUSSION

DR. RALPH PEMBERTON, Philadelphia: Since recognition of the agency of focal infection in arthritis, we must agree that the pendulum has swung heavily to the bacteriologic end. In our series of 400 cases, we were unable to relate to impaired renal function the benefits most writers ascribe to eliminative procedures. In respect to uric acid, the evidence Dr. Chace introduces tends strongly to get away from the remnants of the belief that it plays an important rôle in this disease. Apropos of this question, I feel more and more that there is much in common between arthritis and gout. The point which has interested me most, perhaps, in Dr. Chace's paper has been the suggestion he made as to the action of the salicylates upon the circulatory system. Dr. Hendrix, Miss Crouter and I have been interested in the respiratory function of the blood, and we have made the observation that if the normal person is compared with the chronic arthritic, there may be found a higher percentage saturation of oxygen in the blood of the latter. With con-

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valescence there seems to be a tendency for that percentage to drop back toward its normal value. The normal individual shows, roughly, a percentage of perhaps 46 or 47. The arthritic runs about 18 per cent. higher. Indeed, he may go very much higher than that. The same phenomenon of a rise in percentage saturation with oxygen takes place in cases in which there is a lowered sugar tolerance, when the blood is examined during the course of that test. We have been rather driven to the conclusion that while this may be referable to a lowered metabolism, it is easy to explain it on the basis of a change in the circulation: whether a vasoconstriction is hard to say. Hoover has shown that various toxins and poisons have the property of inducing capillary constriction, and Rosenow stated that in some experiments on streptococcal arthritis on rabbits there has been found in the tissues adjacent to the joints a very distinct vasoconstriction. I am making so bold as to suggest that part of the phenomena of arthritis may be referable to the oxidative disturbance consequent on such conditions. It is my belief that most types of arthritis tend to a common pathologic basis. Furthermore, I believe it justifiable to relate both acute and chronic arthritis or "rheumatism" to the same underlying pathologic condition. although they do not present the same syndrome clinically.

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VI. THE EFFECT OF DIGITALIS ON THE AUTOMATICITY OF THE PRIMARY CARDIAC PACEMAKER *

B. H. SCHLOMOVITZ, M.S., M.D.
MILWAUKEE

This paper continues our reports on the reaction of the specialized tissue to certain pharmacologic agents. A study of the literature has failed to disclose studies of the effects of digitalis on the mammalian heart in which attempts were made to simultaneously influence the response of the primary cardiac pacemaker or sino-auricular node by localized warming of the node during the therapeutic and toxic stages of digitalis administration.

METHOD

Twenty-four animals (nineteen dogs and five cats) were experimented on in a first series in which only suspension tracings were taken, and in addition a number of experiments in which electrograms and second lead electrocardiograms were taken as a second series. In a third series, the ventricular volume was recorded. The weights of the animals ranged from 1 to 20 kg. Ether was administered, a tracheotomy was done and the thorax was opened under artificial respiration. The phrenic nerves were cut, and the pericardium sewed back to adequately expose the heart. A ligature, inserted in the adipose tissue of the auriculoventricular groove, was used to pull the heart gently to the left, thereby exposing the region of the great veins and right auricle. The exposure was similar to that shown by Schlomovitz and Chase.[1] A receiving tambour con-

*From the Physiological Laboratories of the Universities of Marquette and Wisconsin Medical Schools.

1. Schlomovitz and Chase: Arch. Int. Med. **20**: 613 (Oct.) 1917.

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nected by air transmission to a recording tambour received the auricular movements, the rate, from the appendix of the right auricle. A similar system was connected with the right ventricle. To a certain extent such a system registers the force of the beat. Time was recorded in fifths of a Jacquet chronometer, and in 0.02 seconds by an electromagnetic tuning fork. A normal record on a rapidly moving Hipple electrical kymographion was taken, and then a thermode (1) was applied to the sino-auricular node for a definite time interval. When electrocardiographic records were taken, we then used an all-glass thermode. Digitalis or strophanthin solutions were given intravenously, and the responsiveness of the node noted from time to time until the heart stopped. The solutions were not given continuously, except in the ventricular volume experiments (third series) . The digitalis solution was made up from the tincture, previously assayed, biologically, with a portion of the alcohol replaced by 0.9 per cent. normal saline. The strophanthin solution was made up from amorphous strophanthin. The delicacy of the temperature method in influencing the cardiac pacemaker received a critical presentation in 1. In thirteen of the experiments atropin sulphate was given before or immediately after the beginning of digitalis administration.

RESULTS

The effect of digitalis on the heart rate without atropin and when atropin was given, immediately before or early after digitalis administration, did not yield comparable results for either series, as indicated by Table 1, except that in about 50 per cent. no change could be noted in either. With atropin (twelve experiments), six showed no change in rate, two had a decrease, and four were increased. When no atropin was given (seven experiments) three showed no change in rate, three had a decrease, and only one was increased.

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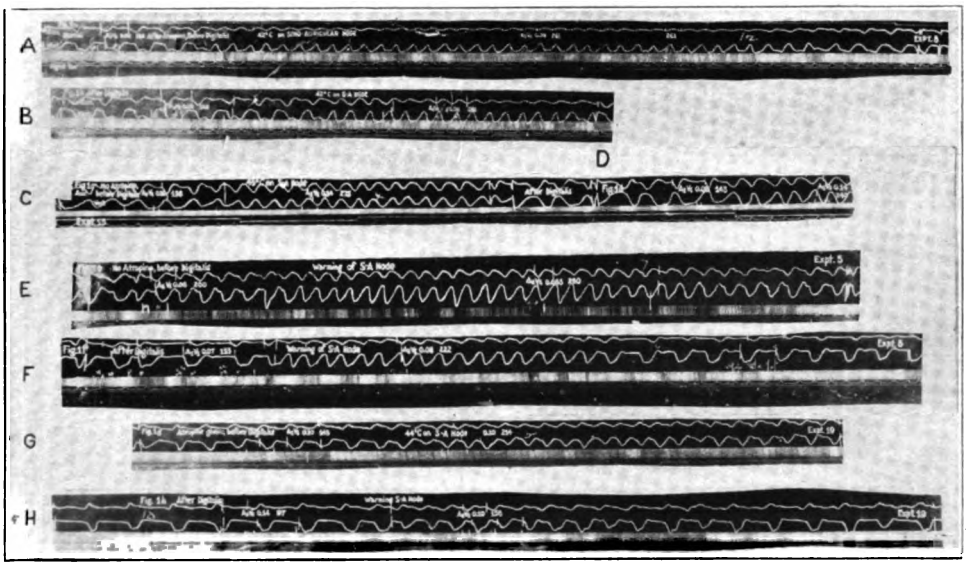

Fig. 1.—Downstroke indicates systole. The upper curve is auricle, the lower is ventricle. Time is shown in fiftieths and fifths of a second.

1*a*, Record from Experiment 8. Rate 136 after atropin and before digitalis was given. On warming, the rate was increased to 261 per minute.

1*b*, Experiment 8. This record shows increased force of beats produced by digitalis. The rate 133 per minute is increased on warming as before to 261. The As Vs interval was unchanged throughout.

1*c*, Experiment 13. No atropin given. Normal heart rate of 158 increased on warming to 273 per minute.

1*d*. Digitalis produces marked increase in force of the beats. Warming increases the rate from 143 to 240 per minute.

1*e*, Experiment 5. No atropin was given. The normal rate of 200 was increased on warming to 250 per minute. Then digitalis was given and the rate dropped to 133 per minute, as shown in 1*f*. Warming now increased the rate to 222 per minute. The As Vs interval was not materially altered.

1*g*, Experiment 19. Atropin was given. Rate of 143 per minute was increased to 214 on warming. After digitalis was given, the rate as shown in 1*b* dropped to 97 per minute, and the As Vs interval was increased from 0.10 to 0.14 second. On warming, the rate was increased from 97 to 158 per minute.

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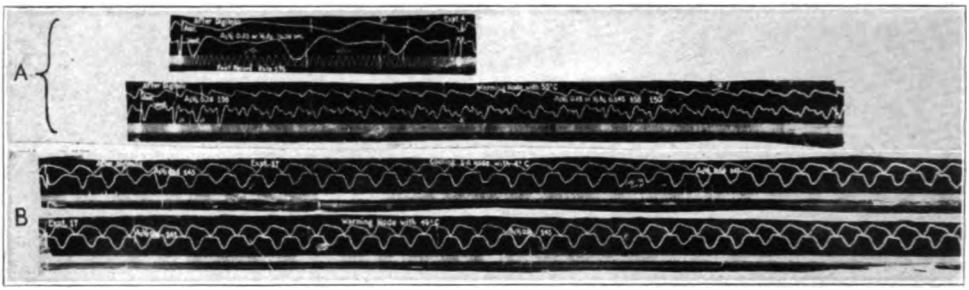

Fig. 2.—*2a*, Experiment 4. A fast and slower record are shown after digitalis has become effective. Warming produces no change in rate.

2b, Experiment 17. Both tracings are taken in advanced digitalization with 1: 1 sequence present, beats equal and regular, and a long As Vs interval 0.16 to 0.18 second, although the heart beat at 143 per minute. However, neither warming nor cooling had an effect on the rate.

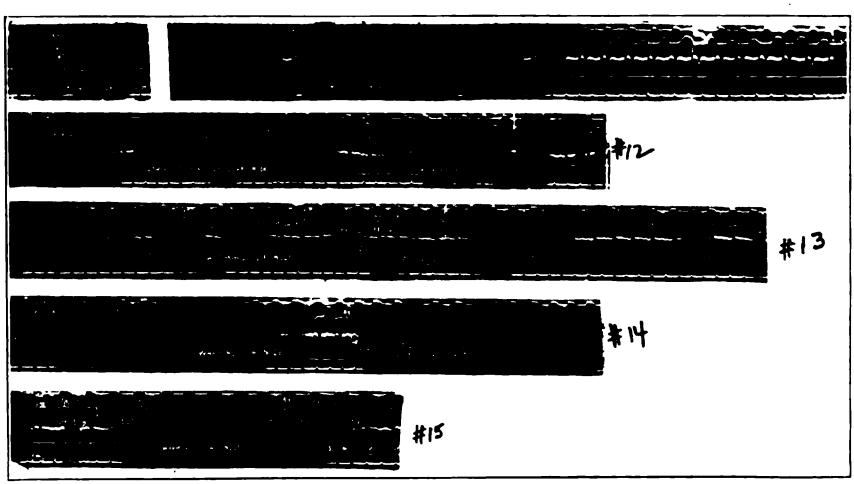

Figure 3

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Under advanced ether anesthesia the tonus of the vagal mechanism as shown by Reid Hunt is reduced leading to an increase in heart rate; but if the ether anesthesia is just sufficient, the rate need not be materially altered. It is the latter rate which is considered the norm in our experiments, and it compares favorably with the rate that prevails in the normal resting animal (dog or cat). Of the experiments not included in Table 1, one heart passed over very early into auricular fibrillation, two hearts were digitalized from the very start, two were studies of the vagus response before, during and after warming of the sino-auricular node, and the rest were studied with the electronegative method.

TABLE 1.—EFFECT OF DIGITALIS ON THE HEART RATE

	With Atropin		Without Atropin	
	Number of Experiments	Per Cent. of Twelve	Number of Experiments	Per Cent. of Seven
No effect	6	50	3	43
Decrease	2	16	3	43
Increase	4	34	1	14
	12	100	7	100

The change in rate not furnishing a single adequate criterion that the therapeutic stage of digitalis was present as shown in Table 1, it was necessary to get additional evidence from the force of the beat as shown by the swing on the levers from diastolic to systolic phase, the effect on conduction (A_sV_s interval), the duration of systole, the change in cardiac tonicity, and the presence of a 1:1 sequence. Our method made impossible the simultaneous recording of ventricular minute volume which is usually increased by digitalis. The criteria for recognizing the therapeutic stage after digitalis is administered in the normal heart in situ under anesthesia have been recently presented and reviewed by Cushny[2] in his usually thor-

2. Cushny: Pharmacol. & Exper. Therap. 11: 103 (March) 1918.

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ough manner. Rothberger and Winterberg[3] rather arbitrarily divide the toxic from the therapeutic stage by the onset of ventricular automaticity. The effect on conduction is evidently the most striking phenomenon in human normal hearts[4] that can be found with our current methods.

It is an established fact that the heart is immediately and markedly accelerated by warming the sino-auricular node, or slowed by cooling the node. This practically amounts to localization of the primary cardiac pacemaker. These results are also obtained after it is evident that digitalis has affected the heart by increasing the force of its beat and its conduction time, or, in other words, when the therapeutic stage prevails the primary pacemaker is still located at the sino-auricular node. Figure 1, Record 1 *a* (Experiment 8) shows the rate increase produced by warming after atropine, and record 1 *b* shows the same rate increase (100 per cent.) after digitalis has increased the force of the beat. The downstroke in the records indicates systole. Record 1 *c* is the normal, and 1 *d* (Experiment 13) shows the effect of digitalis on the force of the beat in a heart not previously atropinized. Warming of the node is equally effective in 1 *c* and 1 *d*. In record 1 *e* and 1 *f* (Experiment 5) no atropin was given. Digitalis produced a marked decrease in rate 200 to 133 per minute, while A_sV_s interval was not materially changed. Still warming was very effective in both. On comparing record 1 *g* and 1 *h* (Experiment 19) it is seen that digitalis after atropin administration produced a decrease in rate and an increase in A_sV_s interval, but warming the node resulted in the same percentage rate increase.

As the digitalis effect increases progressively, the responsiveness of the sino-auricular node is either

3. Rothberger and Winterberg: Arch. f. d. ges. Physiol. **150**: 217, 1913.

4. Cohn, A. E.: J. A. M. A. **64**: 463 (Jan. 30) 1915. Cohn and Fraser: J. Pharmacol. & Exper. Therap. **5**: 512, 1913. White and Satler, J. Exper. Med. **23**: 613.

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gradually diminished or else it disappears abruptly. Table 2 illustrates the gradual diminution that occurred in Experiment 14 from 66 per cent. to 32 to 10, and finally to zero per cent.

When the abrupt loss of responsiveness of the sino-auricular node occurs, then the heart is either in a frankly toxic stage in some experiments, or, in other experiments it is in a phase which would clinically be designated from the standpoint of marked prolongation of conduction time as an advanced but nevertheless good therapeutic digitalis effect. The latter phase

TABLE 2.—GRADUAL DIMINUTION IN EXPERIMENT 14
Experiment 14. No atropin given. Dog, 7.84 kg.

Record No.	Time, Minutes	Procedure	A_sV_s in Sec.	Beats per Minute	+ Increase Beats	+ Increase Per Cent.
5	0	Normal—before warming	0.08	125		
		46 C. on S-A node.....	0.10	200	75	60
	7	Digitalis by vein				
13	21	Before warming.....	0.10	120		
		47 C. on S-A node.....	0.14	200	80	66
15	26	Before warming.....	0.12	120		
		Warming node with 47 C.	0.10	200	80	66
17	34	Before warming.....	0.12	136		
		47 C. on node.....	0.13	180	44	32
18	39	Before warming.....	0.12	136		
		47 C. on node.....	0.14	143	7	5
19	40	Before warming.....	0.14	136		
		47 C. on node.....	0.14	150	14	10
20	43	Before warming.....	0.14	136		
		47 C. on node.....	0.14	136	0	0
After this warming, consistently negative.....					Beats+	Per cent.+

attracted our attention at once in ten experiments because the ventricles follow the auricles regularly with heart cycles equal and similar, and there is nothing to indicate that the pacemaker has disappeared from the node by an inspection of the suspension tracings only. As a rule A_sV_s interval is longer than in the normal heart. We found this to be the case in Experiments 4, 6, 7, 14, 16, 17, 19, 20 and 21. In Table 3 are included a few examples showing a negative reaction of the node on warming or cooling when a lengthened A_sV_s and 1 : 1 sequence prevails.

The same facts are deducible from Figure 2 *a* and Figure 2 *b*. In 2 *a*, taken from Experiment 4, the

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increases produced by warming before digitalis was administered ranged from 15 to 32 per cent., while in Experiment 17 from which Figure 2 *b* is taken the increases ranged from 20 to 40 per cent. Later, with digitalis, there is no perceptible change in rate on warming or cooling. The fact that this phenomenon occurs in both atropinized and nonatropinized hearts shows that digitalis has not only the well-known marked effect on the junctional tissues other than that produced indirectly by the vagus, but in addition induces a condition by which the primary cardiac pacemaker leaves its normal locus even though the heart appears to be beating normally in what seems to be a good therapeutic stage.

TABLE 3.—NEGATIVE RESPONSE OF S-A NODE IN LATE THERAPEUTIC STAGE OF DIGITALIS

Experiment	Record No.	Procedure	A_sV_s in Seconds	Beats per Minute	Per Cent. Increase
6	22	Before warming	0.26	158	
		54 C. on S-A node	0.26	158	0
7	9	Before warming	0.18	171	
		52 C. on S-A node	0.17	176	0
		After warming	0.22	176	
		After warming	0.22	171	
19	15	Before warming	0.30	111	
		45 C. on S-A node	0.30	111	0

Further corroboration of these results were sought in experiments in which not only a second lead electrocardiagram was taken but also a direct lead or electrogram from the sino-auricular node-coronary sinus regions. As shown by Figure 3, the pacemaker has left the sino-auricular node region by the negative phase appearing at the very beginning of the electrogram where it formerly began with a positive phase. The interval between sino-auricular node lead and coronary sinus lead is now 0.13 to 0.14 second (normal 0.10 second), and the A_sV_s interval is 0.165 second. The suspension tracings show the auricles and ventricles in regular 1 : 1 sequence.

Can any evidence be found to show where or why the pacemaker has gone when the sino-auricular

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node does not respond to warming or cooling in advanced digitalization of the heart beating regularly and in 1 : 1 sequence? In some cases it can be shown that the rate at this time has been increased somewhat. For example, the following increases are recorded: Experiment 2, 15 to 20 beats per minute; Experiment 9, 20 beats; Experiment 20, 40 beats; Experiment 23, 38 beats, etc. It is possible that in these cases the increased excitability of the cardiac musculature may cause the beat to arise at an ectopic focus and be developed at an increased rate. However, the increase is never more marked than that which occurs with accelerator stimulation, and it is known that the pacemaker is known to be in the node during accelerator stimulation. On the other hand, in a number of experiments the rate was distinctly slower when the node did not respond to changes in temperature, and at the same time the A_s V_s interval was markedly prolonged (Experiment 4, 21, 6, 15, 16 and 17; in only 4 and 21 was atropin given). Increased excitability of the musculature can still be cited as the cause of the ectopic focus and marked conduction delay as the cause of the slow beat, but there is at present no definite proof that such is the case. It is significant that in Experiment 9 auricular flutter could be induced very easily on warming the node, showing ectopic origin of the beat and indicating that there was some depression in the node. The fact that after digitalis in some of the experiments there was a progressive decrease in the effect on rate produced by warming the node hints at a depression of the specialized tissue. For example, in Experiment 14, the same temperature was repeatedly applied to the node and the percentage increases in rate dropped progressively from a sustained normal of 66 to 30 per cent. and finally to 5 per cent. of the normal.

It has long been known that the A-V node and bundle are depressed functionally by digitalis. It has been our experience that merely exposure of the heart as in these

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experiments does not depress the specialized tissue even when such exposure lasts from five to twelve hours, and the node is being warmed at rather frequent intervals.

The electrograms which were taken by us simply indicate that when warming of the node is ineffective then the pacemaker has left the node.

TABLE 4.—DOSAGE OF DIGITALIS GIVEN BEFORE NEGATIVE EFFECT APPEARED

Experiment	Mg. per Kilogram	Minutes Before Negative Effect Was Shown
17	7.8	21
19	8.1	17
20	8.6	24
14	8.9	22
16	9.5	2+ given as one dose
4	11.0	46
9	13.4	14
13	16.3	9
8	19.0	20
5	20.0	4
11	21.4	16
3	23.8	5
10	27.7	8
18	5.3	Warming still effective after 66 min.
4	7.5	Warming still effective after 57 min.

Experiment 7 of our series is illustrative as one of the controls in that the animal was given digitalis at once by direct injection into the right ventricle. Warming or cooling the sino-auricular node had absolutely no effect on the cardiac rate. In Experiment 12, auricular fibrillation prevailed from the very beginning of the experiment, and warming had no effect either before or after the administration of digitalis. Atropin was not given. After digitalis, the cardiac rate was increased from 150 to an average of 200 per minute.

Table 4 illustrates the dose of digitalis from a single preparation required before warming or cooling had no effect on the sino-auricular node.

COMMENT

There was an element of surprise in finding that digitalis exerted a *late* effect on the sino-auricular node, just before the heart passed over into the toxic stage.

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Taking for granted that the same concentration of digitalis came in contact with the node as with the cardiac tissue proper, and knowing that there is a very good blood supply to the node, there is a reasonable expectation that the node show changes at least as soon as the musculature and conductive junctional tissue. However, this is not the case. Our facts really show that the specialized tissue is divorced from the dynamic (contracting) tissue in accord with the findings in Paper IV[5] of the series, and that digitalis influences the functions of contractility and muscular irritability at first, then the function of conductivity, but certainly not the function of impulse initiation until very late. This again emphasizes the stability of the pacemaker.

The problem that arises concerning the point of origin of the beat late in the therapeutic stage when to all intents the heart is beating rhythmically, regularly, in 1 : 1 sequence but with a long A_sV_s or P-R interval and absence of the pacemaker at the node is of great interest.

It has been indicated in the data above that the increase in muscular excitability may be the cause of ectopic beats, but the seat is evidently well localized in specialized tissue because the beats are so rhythmic and the A_sV_s intervals equal throughout. We have previously indicated (Paper V[6] of our series) that ventricular tachycardia can be produced by localized warming of the ventricle in advanced digitalization of the heart. Such excitability can also apply to auricular tissue.

In the normal rabbit's heart, Lohmann secured auriculoventricular rhythm as a result of the application of formaldehyd to the mouth of the superior vena cava. Brandenburg and Hoffmann later proved the pacemaker to be in the region of the auriculoventricular node when it disappeared from the sino-auricular node.

5. Schlomovitz: Am. J. Physiol. **55**: 462, 1921.
6. Schlomovitz: Am. J. Physiol. **55**: 485, 1921.

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In their review of the literature by Eyster and Meek [7] it follows clearly that the pacemaker normally has its site in some part of the specialized tissue. In the normal heart some conclusion can be made as to where the pacemaker is by simultaneous inspection of the lengths of A_sV_s intervals, but in the case of the digitalized heart the A_sV_s interval loses its value as a special criterion because it also is altered by the digitalis. There are therefore at least two simultaneous variables—A_sV_s interval and removal of the pacemaker, with the resulting confusion in reference to the point of origin of the pacemaker. The following hypotheses can be advanced. (1) It is coronary sinus rhythm. (2) It is nodal or atrioventricular rhythm with a long A_sV_s interval somewhat similar to the tracings in the asphyxial condition described by Lewis.[8] (3) It is an ectopic auricular rhythm. (4) It is a marked A_sV_s rhythm with the beat ventricular in origin, somewhat similar to the view advanced by Rothberger and Winterberg [9] on the importance of the tertiary (?) centers. In any event a study of suspension tracings alone would be entirely misleading. Studies of the axial electrocardiograms may show at the most the presence of a levogram or dextrogram. Ours were apparently levograms. A part of the ideal method to solve this problem would be the use of many "differential electrodes" [9] so as to localize the point of initial negativity.

Selenin,[10] using the oesophageal-anus lead, and administering digitalin and digitoxin, believes that in the toxic stage the beat is similar to that seen in left ventricular extrasystole, and that the P wave disappears indicating auricular paralysis. Rothberger and Winterberg,[8] taking the same indirect lead, stated their desire to study the effect of strophanthin on the automatic centers of

7. Eyster and Meek: Physiol. Rev. **1**: 1 1921.
8. Lewis: Mechanism and Graphic Registration of Heart Beat, Ed. 2, p. 167.
9. Clement: Ztschr. f. Biol. **58**: 110, 1912.
10. Selenin: Arch. f. d. ges. Physiol. **143**: 137, 1911.

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the heart. They employed section and stimulation of the extrinsic cardiac nerves as aids in analysis of the processes. They expressly state that the sinus node dominates in the therapeutic stage, and that in the toxic stage the beats arise directly from the tertiary (?) centers in the ventricles. However, there is at the beginning stimulation of the sinus node and finally injury, depending on the size of the dose. They postulate a stimulating effect because of an increase in rate, but they also say that maximum rates were obtained with doses of strophanthin not far removed in amount from the toxic dose. The toxic dose inevitably resulted in a dissociation stage with ventricular automaticity. It will be noted that we also found a faster rate late in the therapeutic stage, but that warming the sino-auricular node at this time has no effect on the heart rate. It is to be questioned, therefore, whether Rothberger and Winterberg obtained stimulation of the accelerator mechanism as they claim.

Our knowledge at the present time in reference to the significance of the variations in the P wave is not sufficient to allow us to make definite conclusions about either increased or decreased irritability of the sino-auricular node. Therefore a final decision concerning data obtained by indirect leads by workers from the time of Straub, 1909, to Robinson, 1918,[11] cannot be made.

An interesting method was used by Shigeru Sakai[12] on the isolated, excised heart preparation. Rabbits' hearts were perfused, and an electrogram was taken with one lead attached to the sulcus terminalis and one lead to the apex of the heart. In addition, suspension tracings were taken of both an auricle and a ventricle. The digitalis series and other drugs were used in 104 experiments. Tracings were taken every thirty sec-

11. Straub: Ztschr. f. Biol. **53**: 106, 1910. Robinson and Wilson: J. Pharmacol. & Exper. Therap. **10**: 491, 1918.
12. Sakai Shigeru: Mitt. a. d. med. Fak. d. k. Univ. Tokyo, **19**: 245, 1918.

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onds. Following acceleration of the beat there occurred reversed rhythm during which period the P wave was diphasic and evidently heterotopic, and a small R-P interval indicated auriculoventricular rhythm. Later the stage appeared in which the tertiary centers (Sakai follows Rothberger's nomenclature) initiated the beat. Sakai's work is the only one which we found exclusive of our own in which the electronegative changes were studied by leads taken directly from the heart.

SUMMARY

1. The sino-auricular node in the intact mammalian heart in situ is markedly responsive to warming or cooling early in the therapeutic stage of digitalis.

2. (*a*) In some cases the node loses its responsiveness gradually later in the therapeutic stage when the beats are regular, rhythmic and either faster or slower than normal, with 1 : 1 sequence, and a markedly prolonged A_sS_s interval. The heart still later shows very toxic signs.

(*b*) In other cases the unresponsiveness of the node is established when the toxic stage is evident.

3. Where the beat has its origin when the condition described above under *a* arises cannot at present be definitely indicated.

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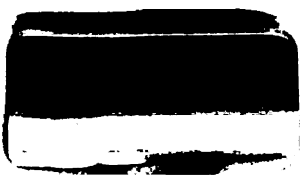

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